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ARCHIVES OF OPHTHALMOLOGY

VOLUME 40 (old series Volume 97) OCTOBER 1948 NUMBER 4

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THE BLINDSPOT SYNDROME

KENNETH C. SWAN, M.D.
PORTLAND, ORE.

IN 1947 a squint syndrome was described in which the physiologic blindspot, created by the optic papilla, seems to play an especial role.[1] Recognition of this syndrome resulted from a study of the field of binocular vision in 296 cases of concomitant esotropia in older children and adults. For distant fixation the physiologic blindspot of the deviating eye was found to overlie the point of fixation in 80 cases; i. e., the deviation was 12 to 18 degrees. In most of these cases the physiologic blindspot was only part of a suppression scotoma and its position was inconstant; however, there were 7 cases in which it seemed probable that the physiologic scotoma provided the essential mechanism for the alleviation of diplopia and played an important role in maintaining the esotropic state. These 7 cases had in common certain symptoms and signs, and the responses to treatment and clinical courses were similar. This group of cases seemed to represent a clinical entity, which was designated as the "blindspot syndrome" (fig. 1). Since the initial report of 7 cases was submitted for publication, an additional 95 cases have been observed in which the physiologic blindspot of the squinting eye seemed to play the major role in alleviation of diplopia, i. e., acted as a central scotoma in the field of binocular vision. It is the purpose of the present report to review this larger series of cases in order to establish more definitely the circumstances in which this mechanism develops and to determine how it influences the clinical features, course and treatment of concomitant esotropia.

To appreciate the possible role of the blindspot in concomitant esotropia, it is necessary to understand the mechanism of diplopia. In the presence of normal retinal correspondence and in the absence of suppression, diplopia theoretically results whenever grossly dis-

From the Department of Ophthalmology, University of Oregon Medical School.

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1. Swan, K. C.: A Squint Syndrome, Arch. Ophth. **37**:149-154 (Feb.) 1947.

parate retinal areas receive a similar stimulus. In reality, most persons are aware of seeing double only the object of conscious regard, i. e., the point of fixation and the immediately surrounding area. Diplopia in the peripheral fields may play an important role in the mechanism of binocular vision, but the normal person is little aware of peripheral double images when the eye is mechanically displaced. He may alternately fix with either eye, but his attention is on diplopia of the "object or area of regard."

Most patients with long-standing, untreated concomitant esotropia are not aware of diplopia because the object or area of regard is perceived monocularly. Travers [2] expressed the belief that this monocular perception of the object of regard was due to suppression of the image

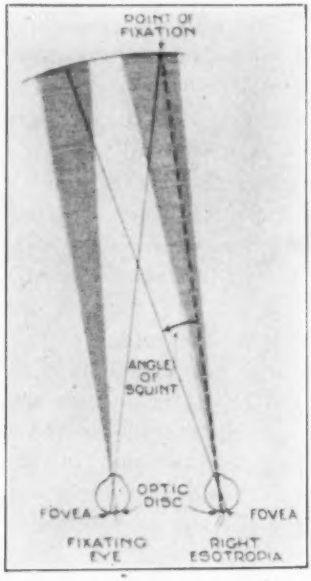

Fig. 1.—Mechanism of the blindspot syndrome, characterized by periodic diplopia, concomitant estropia, physiologic blindspot of the squinting eye overlying the point of fixation, hypermetropia or anisometropia, normal retinal correspondence and usually some amplitude of fusional movements.

of the peripheral retina of the squinting eye; however, in cases of the blindspot syndrome rays of light from objects fixated by the fovea of the fixating eye largely fall on the optic papilla of the squinting eye. In such instances an absolute scotoma, the physiologic blindspot, is provided by nature to cover, at least partially, this area of regard.

LOCALIZATION OF BLINDSPOT OF DEVIATING EYE

There are several methods of localizing the physiologic blindspot of the deviating eye in the field of binocular vision. It is obvious that

2. Travers, T. a'B.: The Origin of Abnormal Retinal Correspondence, Brit. J. Ophth. **24**:58-64 (Feb.) 1940.

in most cases an esotropia of 12 to 18 degrees results in the areas of the field of binocular vision corresponding to the fovea of each eye being overlapped by the physiologic blindspot of the opposite eye. In cases of the blindspot syndrome, this deviation may be a degree or two greater or less, apparently in accordance with whether or not there is a peripapillary area of retinal suppression to enlarge the scotoma in the field of binocular vision. A considerable degree of hypertropia may also occur. For near fixation, the deviation of the eyes from parallelism would have to be correspondingly greater if the blindspot were to be utilized for the alleviation of diplopia but the deviation as measured by the cover test would remain unchanged. Stated otherwise, if a patient has concomitant esotropia of 10 to 20 degrees, rays of light from the area of regard are largely falling on the blindspot of the

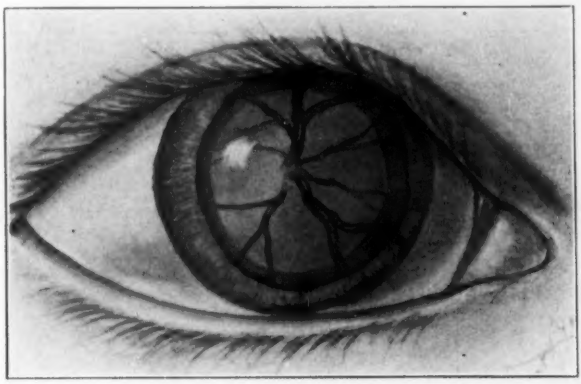

Fig. 2.—Viewed with the ophthalmoscope at a distance of 6 to 10 inches (15 to 25 cm.), the optic papilla of the deviating eye appears to fill the pupillary area in a case of the blindspot syndrome.

squinting eye and the object of regard, at least in part, is being viewed monocularly.

A second means of determining the position of the blindspot is ophthalmoscopy. While the patient fixates a distant point of light, the examiner places himself directly in front of the deviating eye and focuses on the fundus from a distance of 6 to 10 inches (15 to 25 cm.). In cases of the blindspot syndrome, an enlarged image of the nerve head will almost completely fill the pupillary area (fig. 2).

A third method of determining the usual position of the blindspot is to plot the field of vision of the deviating eye while the other eye is fixating. To do this, it is necessary to separate the images of the two eyes, either by a mirror and two screens or by filters and twin projectors. Either polaroid or red and green filters of the type described by Lancaster may be used with two projectors to separate the targets

presented to the two eyes.[3] The blindspot of the squinting eye is plotted on a large screen in an illuminated room to simulate as nearly as possible the usual visual conditions. With the Lancaster red and green filter–twin projection system, it frequently has been possible to plot the central field of binocular vision in children of preschool age by the method to be described.

The degree of esotropia is measured in the usual manner and the patient is asked, while wearing the color filters, to adjust the direction of one of the projectors until the red and green images appear superimposed on the screen. In the presence of normal retinal correspondence the separation of the targets on the screen will be in accordance with the deviation of the patient's eyes. Then the blindspot is localized in the monocular field of vision with particular reference to the distance between the point of fixation and the center of the blindspot. If

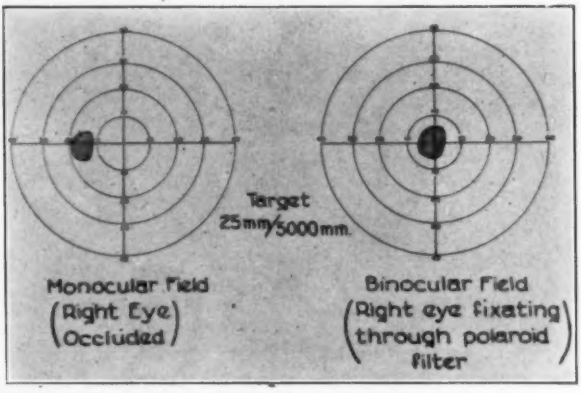

Fig. 3.—Position of the physiologic blindspot of the deviating eye in a case of concomitant left esotropia of 14 D.

this angle is equal to the previously determined deviation of the eyes, it is evident that the blindspot of the squinting eye overlies the point of fixation in binocular vision. Further confirmation can be obtained by actually localizing the blindspot in the field of binocular vision. In cases of the blindspot syndrome, an absolute scotoma the size and shape of the blindspot can usually be demonstrated to overlie the point of fixation (fig. 3). For this reason, only one target is visualized by the patient when the two targets are superimposed on the screen (fig. 4).

An adjustable haploscopic device, such as the major amblyoscope, provides still another means of localizing the blindspot of the squinting eye. In most cases of the blindspot syndrome an area of monocular perception measuring 5 to 8 degrees in horizontal diameter will be

3. Lancaster, W. B.: Detecting, Measuring, Plotting and Interpreting Ocular Deviation, Arch. Ophth. **22**:867-880 (Nov.) 1939.

found when the instrument is adjusted to the region of orthophoric position (fig. 5); however, this is not a constant finding because the instrument gives the patient a sensation of nearness and, therefore,

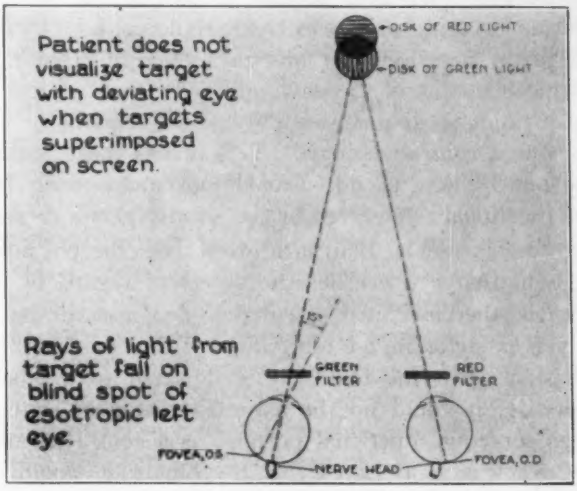
Patient does not visualize target with deviating eye when targets superimposed on screen.
DISK OF RED LIGHT
DISK OF GREEN LIGHT
15°
Rays of light from target fall on blind spot of esotropic left eye.
GREEN FILTER
RED FILTER
FOVEA, OS
NERVE HEAD
FOVEA, O.D

Fig. 4.—Use of red-green filter–projection system to localize scotoma of the deviating eye in a case of the blindspot syndrome.

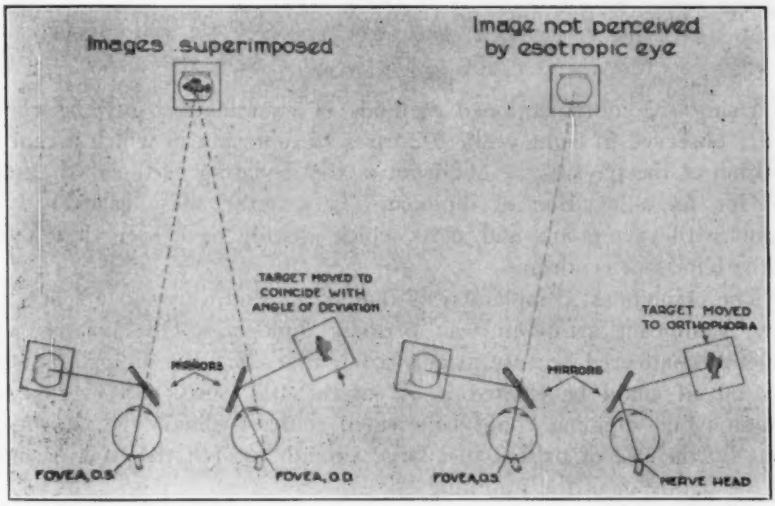

Fig. 5.—Examination with the major amblyoscope in a case of the blindspot syndrome, with esotropia of 15 degrees.

often stimulates a position of greater esotropia than is present under usual visual conditions. Moreover, accurate plotting of the vertical measurements of the blindspot is awkward with the major amblyoscope.

For these reasons, the major amblyoscope is less satisfactory than filter–twin projection systems for localization of the blindspot of the deviating eye.

In some patients it has been possible to measure the scotoma created by the blindspot by using prisms to create diplopia, i. e., by determining the size of prism necessary to shift rays of light from the point of fixation off the blindspot of the deviating eye. In many patients, however, prisms stimulate disjunctive movements, apparently to maintain the blindspot as a central scotoma. This occurs most commonly with prisms base out. These pseudofusional movements seem further evidence of the functional role played by the blindspot as a central scotoma.

It might be coincidental that, in a given case, the physiologic blindspot of the squinting eye overlies the object of regard in the field of binocular vision; therefore, it is essential to demonstrate that the blindspot actually is a factor in the alleviation of diplopia by the induction of double vision when the blindspot is deviated to another position. Stated otherwise, it could not be assumed that the blindspot of the squinting eye served a functional purpose as a central scotoma simply because the eye was so deviated that the blindspot would overlie the object of regard in the field of vision. It would be necessary to prove this supposition by using prisms or other devices to displace the blindspot of the squinting eye from the central area, and thereby creating double images of the object of regard in ordinary visual circumstances.

OBSERVATIONS

Using the aforementioned methods of examination, my associates and I observed in eight years 102 cases of esotropia in which a central position of the physiologic blindspot of the deviating eye seemed essential for the alleviation of diplopia. In general, these cases had in common the symptoms and signs which already have been designated as the blindspot syndrome.

The commonest complaint was that of a "slight cross-eye," but the most significant symptom was periodic diplopia. This history was seldom volunteered because in only a few cases was the diplopia annoying, but it could be elicited in 75 of the 102 cases. In every case homonymous diplopia could be created under ordinary visual conditions by the use of prisms just large enough to shift the rays of light off the blindspot of the squinting eye.

The most obvious sign was concomitant esotropia, of 10 to 20 degrees. The average deviation was 14 to 16 degrees for distant fixation. The deviation from parallelism was proportionately greater for near fixation, but greater variations were found.

In the first report of blindspot syndrome, it was observed that hypermetropia or anisometropia was present in all 7 cases. Analysis

of the refractive error in the additional series of cases seems to confirm the importance of this observation. Of the 102 cases, hypermetropia of more than 2 D. or anisometropia of more than 1 D. was present in 62, a higher degree and higher incidence of these refractive errors than is generally reported to occur with esotropia. This suggests that the hypermetropia or anisometropia is a common part of the blindspot syndrome, but analysis of a larger series of cases, with a concurrent study of the refractive error in a control series, will be necessary definitely to establish this fact.

Normal retinal correspondence seems a consistent feature of the blindspot syndrome. It could be demonstrated by the usual methods of examination to be present in all cases.[4] In some of our cases of anomalous correspondence, rays of light from the point of fixation seemed to fall on the blindspot of the esotropic eye, but diplopia could not be elicited under ordinary visual conditions in a single case of this group when the blindspot of the deviating eye was displaced from the central area. Our studies of the role of the blindspot in anomalous correspondence are not yet conclusive; however, they indicate that, although the physiologic blindspot may function as a part of the suppression scotoma, it does not play as important a role in the alleviation of diplopia as in cases of normal retinal correspondence.

In the initial orthoptic examination, the images of the two eyes could be fused into a single mental impression in less than one-half the 102 cases of the blindspot syndrome, and only a few had fusional movements of appreciable degree when the targets were adjusted to their deviation on a haploscopic device, such as the major amblyoscope; however, this sensory and motor fusional ability could be established in all the remaining cases in which orthoptic training was feasible. Good fusional potentialities can, therefore, be considered a part of the blindspot syndrome.

The symptoms and signs of the blindspot syndrome in the larger series of cases seem the same as in the initial group of 7 cases. An analysis of the circumstances in which this syndrome develops is of significance in determination of the role of the physiologic blindspot in esotropia.

In 32 cases in which there was no previous treatment the blindspot syndrome was evident on admission. In 22 of these cases there was an average spherical refractive error which was slightly less than 3 D. of hypermetropia with an associated astigmatism of approximately 1 D. The consistent finding of an appreciable degree of hypermetropia would seem to indicate that this refractive error was an important factor in the development of esotropia in these cases. The onset of

4. Swan, K. C.: Definition of Anomalous Retinal Correspondence, Am. J. Ophth. **28**:58-61 (Jan.) 1945.

esotropia in this group of cases was also of significance. In about one-half the cases the first manifestation of anomaly was a periodic esotropia, becoming manifest at 2½ or 3 years of age in association with fatigue or illness. In the other one-half the onset of esotropia was early in infancy. In several of the latter group no treatment was given because during the first few years of life the esotropia seemed to be improving spontaneously. In these cases it is likely that the patients initially had a considerable amount of esotropia and then slipped into the "blindspot" syndrome when the deviation decreased.

In a second group, of 18 cases, the "blindspot" syndrome was not evident on admission. All the patients were children, with an average age of 7½ years. In these children the blindspot syndrome was not definitely acquired until correcting lenses were prescribed in our clinic. On admission, the average deviation was from 25 to 27 degrees of esotropia for distant fixation, but the deviation for near fixation was considerably greater. The average amount of hypermetropia in these cases was larger than that found in the remaining 82 cases of the blindspot syndrome, averaging almost 3.5 D., with an average of 1.25 D. of astigmatism. A history of diplopia was elicited in one third of these cases during the first week after glasses were prescribed. It is apparent from this group of cases that an appreciable number of patients with so-called accommodational squint who have a relatively large degree of esotropia slip into the blindspot syndrome when the prescription of correcting lenses effects only a partial reduction of the deviation.

In 17 cases of esotropia the blindspot syndrome developed after an operation which did not fully correct a deviation of 25 degrees or more for distant fixation. In 16 of the 17 cases normal retinal correspondence was evident before operation, and in the remaining case correspondence became normal after surgical intervention. For comparative purposes 98 cases of esotropia with anomalous correspondence were studied in which operation had been performed for purely cosmetic purposes. With the exception of the 1 case in which correspondence became normal after operation, in none of this group could it be demonstrated that the patient was utilizing the blindspot after operation for the alleviation of diplopia.

In a fourth group, of 8 cases, the blindspot syndrome seemed to develop in association with the establishment of normal retinal correspondence. In 2 of these 8 cases normal retinal correspondence developed during periods of alternate monocular occlusion. In the other cases occlusion and "macular massage" were required. With the development of normal retinal correspondence and the discontinuance of occlusion, the eyes acquired the typical deviation of the blindspot syndrome, and diplopia could be created with prisms displacing the blindspot of the squinting eye from the central area.

In another group, of 4 cases, the blindspot syndrome developed after the correction of amblyopia in the esotropic eye. In 1 of these cases esotropia had not been noticeable prior to the prescription of an occluder by another physician, who sought to improve visual acuity in the amblyopic eye. After six months of total occlusion, the ophthalmologist observed that visual acuity had improved from 20/200 to 20/30 in the affected eye, but that esotropia had developed and the child had periodic diplopia. On admission the child had all the aforementioned signs and symptoms of the blindspot syndrome. In the other 3 cases a gross esotropia associated with visual acuity varying from 20/70 to 20/300 in the deviating eye was present on admission. Prolonged occlusion in these cases markedly reduced the size of the suppression scotoma in the field of binocular vision and improved visual acuity to 20/25 in 2 cases and to 20/50 in the third case. In none of these cases

Circumstances of Development of the Blindspot Syndrome

	No. of Cases
Associated with uncorrected refractive error	22
Following prescription of glasses for accommodative esotropia	18
Following partially effective operation for esotropia	17
Associated with establishment of normal retinal correspondence	8
Associated with correction of amblyopia	4
Undetermined	33
Total	102

was the blindspot syndrome evident until weeks after occlusion was discontinued.

In 30 cases it was not possible to determine the circumstances in which the blindspot syndrome developed, because in most of them some type of treatment had been received prior to admission. These observations, summarized in the accompanying table, indicate that the blindspot may develop as an initial process in association with an uncorected hypermetropic or refractive error, but that, in the presence of normal retinal correspondence and with an appreciable degree of simultaneous binocular perception, patients with large degrees of esotropia frequently begin to use the physiologic blindspot of the squinting eye as a central scotoma when the deviation is reduced either by surgical intervention or by glasses. Moreover, it seems that a blindspot syndrome may develop in esotropic patients when normal retinal correspondence is first established or when amblyopia and suppression are disrupted by occlusion.

The period of observation is too short for one to determine with certainty the course of the blindspot syndrome, but it seems that once this mechanism for the alleviation of diplopia is established,

unless modified by treatment, it remains unchanged for relatively prolonged periods. Twelve of the 102 patients were adults, and, of this group, 4 had become so well accustomed to their condition that they did not seek correction of the esotropia. One man, aged 44, could remember having had periodic diplopia since childhood. Another adult, with a similar history, is a physician who has been under observation for nearly four years. During this period, the signs and symptoms have remained unchanged. In addition to this group of adults, 11 children have been observed over a period of one and one-half to three years for whom, for various reasons, no treatment other than correction of refractive errors has been prescribed. In these patients the condition has remained unaltered despite the fact that these patients are all rapidly growing, with decreasing refractive errors and changing orbital structure.

That the mechanism of the blindspot tends to remain constant is also evident in analysis of the results of attempted cosmetic surgery in well established cases of the blindspot syndrome. In 24 cases surgical correction was attempted without orthoptic training or measures other than correcting lenses. In only 7 of these cases were there spontaneous development and maintenance of single binocular vision over a period longer than six months. In most of the remaining 17 cases postoperative diplopia was immediately evident, and in all but 5 cases the blindspot syndrome redeveloped within a period of nine months. The significance of this observation will be discussed further in relation to treatment.

The prognosis for the blindspot syndrome is excellent when the condition is recognized and properly treated. Of the 102 cases, therapy was carried to completion in only 38; that is, single binocular vision with bifoveal fixation, stereopsis, a comfortable reserve of fusional movements and establishment of a satisfactory accommodation-convergence relationship under the usual visual conditions was effected. The average period of treatment was seventeen months. In 25 cases treatment is now going on and progress is satisfactory. In a number of cases orthoptic training is being deferred until the child is old enough to cooperate fully with orthoptic measures. Finally, in 10 cases, including 4 of adults, an attempt to restore single binocular vision did not seem justified. In most of these cases the deviation of the eyes was not conspicuous; the patients had adjusted themselves to the periodic diplopia and could perform their visual tasks comfortably. In several of these instances a wide angle kappa in each eye made an actual deviation of the lines of vision of about 15 degrees appear inconspicuous.

Of greater significance than the total number of cases in which single binocular vision has been restored is the fact that not a single

failure has resulted in any case in which the patient was of average intelligence and cooperated in treatment, and in which there was opportunity to carry the treatment to completion.

The number of patients treated is large enough and the period of observation following restoration of single binocular vision sufficiently prolonged to indicate clearly that a combination of corrective measures is essential for the effective treatment of the blindspot syndrome. Exceptions are made to fit the circumstances in the individual cases, but the routine which seems most successful is as follows: As the first step in treatment, the refractive error is fully corrected, and the results are observed for a few days or several weeks. A longer period does not seem justified, for in only 1 of 27 cases in which no previous treatment had been given did the prescription of glasses alone result in the establishment of single binocular vision.[5] This favorable effect became evident within a few days. If correcting lenses create diplopia which cannot be overcome by the fusion mechanism, it is our custom to prescribe a monocular occluder to prevent the patient from slipping back into the blindspot syndrome or acquiring a suppression scotoma before further corrective, e. g., surgical measures can be undertaken.

Muscle surgery seldom seems fully effective unless the patient has an adequate reserve of fusional movements to maintain single binocular vision when the deviation is corrected. The best results have been obtained when operation has been deferred until an appreciable amplitude of fusional movements has been established by orthoptic training. This is administered in the clinic with the major amblyoscope, because the deviation is usually too great to permit the use of simple home training devices, such as the Brewster-Holmes stereoscope or prisms. In a few instances, as little as five or six hours of training, divided into short periods, has been required to establish a wide range of convergence and divergence, with control of accommodation. In a few extreme cases, five or six months of training, with sessions two or three times a week, have been required.

When ample fusional movements have been established, surgical correction of the deviation is conducted in accordance with established principles. It has been our custom to proceed cautiously and to err on the side of undercorrection, but in those few cases in which a slight overcorrection was done the patients have seemed to progress most favorably in their postoperative course. This was to be expected, because it is generally easier to build up the convergence to overcome an exophoria than it is to increase the amplitude of divergence to

5. In this case a considerable esophoria has persisted during the few months that the patient, a 12 year old girl, has been observed. This patient is receiving intensive orthoptic training.

overcome an esophoria. On the other hand, a gross overcorrection is to be avoided. In 1 case the postoperative deviation was 10 D. of exophoria. The child was able to overcome this deviation only with considerable accommodative effort, and even after extensive training was still annoyed by spasms of accommodation after a relatively short period of reading. Orthoptic training may or may not be necessary after operation to establish an adequate reserve of fusional movements and a proper accommodation-convergence relationship. In summary, the optimal degree of surgical correction of the deviation in cases of the blindspot syndrome remains to be established by further experience, but it would seem that correction of the refractive error, establishment of ample fusional ability by orthoptic training and full or slight overcorrection of the esotropia by surgical measures produce most effective immediate results. Another decade will be required to determine the long range results.

COMMENT

It has been the purpose of this report to call attention of other ophthalmologists to the possible role played by the physiologic blindspot in cases of concomitant esotropia and to stimulate further investigation. The cases reported are inadequate in number and the period of observation is not sufficiently prolonged to permit one to speak of this role with finality. In a mechanism which is as complex as binocular vision, there are certain to be factors which have been overlooked. Nevertheless, the evidence that has been compiled in this study is indicative that the physiologic blindspot plays an important role in the alleviation of diplopia in certain cases of esotropia. The term blindspot syndrome has been employed as a means of distinguishing this group of cases for further study in varying circumstances and with different technics.

This study indicates that the blindspot syndrome is relatively common either as an initial condition or as a result of inadequate treatment of larger degrees of esotropia; but no conclusions as to the exact incidence of the syndrome can be drawn from this series of cases. Not only is our series of cases relatively small, but it includes an appreciable number of cases recognized by other ophthalmologists as belonging to the blindspot syndrome, and therefore referred to the University of Oregon for study.

A fact which has become evident in the study of a larger series of cases than were included in the initial report is that it is in distant fixation that the blindspot plays its greatest role in the alleviation of diplopia. In a patient with the blindspot syndrome the deviation for fixation at a distance of 5 meters or greater is surprisingly constant, and the position of the blindspot in the field of binocular vision can be demonstrated to lie constantly in the central field. On the other

hand, localization of the blindspot in the field of vision for near fixation usually is more variable. In some patients accommodative adduction fatigue seemed to play an important role in this variability; and, as a result, several reported an annoying diplopia after doing close work for short periods. In others it was evident that mechanisms other than the blindspot, such as excessive adduction of the nonfixating eye, would occasionally play a role in the alleviation of diplopia for near fixation.

In the blindspot syndrome, it is evident that the fovea of the squinting eye is covered by the physiologic blindspot of the fixating eye; consequently, there are two areas of monocular macular perception in the field of binocular vision in a case of the blindspot syndrome. A question which has frequently risen in relation to this syndrome concerns what happens to the image perceived by the nonfixating fovea. In a number of more cooperative patients with the blindspot syndrome, it was possible to study this relation. When similar targets were presented to the foveal regions on an otherwise blank screen, they were fused; but when dissimilar, conflicting targets were presented, a rather pronounced dominance of one eye was frequently noted and retinal rivalry often could not be demonstrated. One patient occasionally noted a dim second image, different from the object of regard, superimposed on the point of fixation. On examination this proved to be the image perceived by the foveal area of the squinting eye. As yet these studies have been too few to be conclusive, but they indicate that a strong dominance of the fixating eye may be a common feature of the blindspot syndrome. Whether or not a true functional scotoma constantly occurs in the foveal region of the deviating eye, or whether the foveal region simply drops to the level of the surrounding peripheral retina with inattention, remains to be definitely established.

SUMMARY

In a large series of cases of esotropia observed in the clinics of two medical schools, 102 were found to have in common certain symptoms and signs which have been designated as the blindspot syndrome.

Periodic diplopia, a concomitant esotropia of 10 to 20 degrees, physiologic blindspot of the deviating eye overlying the area of regard, hypermetropia or anisometropia, normal retinal correspondence and potentialities for single binocular vision constitute the blindspot syndrome.

In this syndrome the eye is deviated into such a position that the physiologic blindspot of the esotropic eye overlies the point of fixation and the immediately surrounding area (area of regard) in the field of binocular vision. This seems to provide the essential mechanism for the alleviation of diplopia. Diplopia can be created in every instance

by shifting the blindspot off the central area with prisms or some haploscopic device.

The blindspot syndrome may develop spontaneously in association with an uncorrected refractive error. It may also be acquired after partial correction of a larger degree of esotropia, either by glasses or surgically. Occasionally it may develop after a period of occlusion of an amblyopic eye or in association with the establishment of normal retinal correspondence. The blindspot syndrome does not seem to develop in the presence of anomalous retinal correspondence; at least, it cannot be demonstrated to play a role in the alleviation of diplopia in such circumstances.

The prognosis for the restoration of single binocular vision in ordinary circumstances seems excellent in cases of the blindspot syndrome, provided that treatment is adequate. Glasses, surgical intervention or orthoptic training alone is seldom effective. It is necessary to correct the refractive error, to establish an ample range of fusional movements before operation, to correct fully the deviation by surgical means and then to follow operation with orthoptic training in order to establish a reserve of fusional movements adequate to overcome any residual deviation without undue stress on the accommodation-convergence mechanism. An attempt to restore normal binocular vision does not seem justified in an older patient who has visual comfort and in whom a large angle kappa makes the esotropia inconspicuous.

The blindspot syndrome has been described not as a fully established clinical entity but, rather, as a means of calling attention of other ophthalmologists to cases of concomitant esotropia in which the physiologic blindspot of the squinting eye seems to play an especial role in the alleviation of diplopia. It is hoped that study of patients with this disorder in varying circumstances, with different technics and by other ophthalmologists will determine more fully the clinical significance of this mechanism.

University of Oregon Medical School.

ABSTRACT OF DISCUSSION

DR. FRANCIS HEED ADLER, Philadelphia: Dr. Swan has made a valuable contribution in pointing out that this syndrome can be cured in the majority of instances if the treatment is adequate. As a matter of fact, the syndrome may arise in some cases because of inadequate treatment. He has outlined the features which characterize the syndrome, the so-called accommodational squint; they are: an esotropia which is of a small angle, generally under 15 degrees, and concomitant hypermetropia; normal retinal correspondence, and potentialities of binocular single vision. In addition, the two characteristics Dr. Swan pointed out, which are necessarily present in order that the case may be placed in this subgroup of accommodational squint, are (1) that the

patient have periodic diplopia and (2) that diplopia can be elicited by displacement of the image from the blindspot in the squinting eye with prisms. This syndrome is not peculiar in its origin but can be explained by a relatively simple mechanism. A child with an esotropia of 12 to 17 degrees in the horizontal meridian has at all times a natural protection against diplopia because the image on the squinting eye falls on the blindspot of the optic nerve and corresponds with the fixation of the nonsquinting eye; therefore, he is continuously protected against diplopia. One of two things happens: As a result of his growing older, the angle of squint becomes less in some cases, presumably because his hypermetropia decreases. If, then, for natural causes, the angle of squint becomes less, the correspondence of the fovea in the fixing eye to the blindspot is no longer maintained. On the other hand, if the child is operated on later in life, after the age of 5 years, he is presented with a new situation; if the operation is not entirely complete and does not result in a fovea-to-fovea relation, the child is faced with the choice of having diplopia and accepting it, of learning suppression or of returning to his previous angle of squint.

In Dr. Swan's first series of cases, which he reported a few years ago, there was no patient under the age of 8 years. The diplopia came on at about school age, and it was obvious that the reason, in the cases in which it came on of itself, was that the angle of squint had diminished; the child was now presented with diplopia at a later age and had to learn suppression. Suppression is not easy to learn after the age of 5; so this syndrome appears after this age.

In those cases in which the condition followed operation, the surgical treatment was inadequate. In all cases which the author reported previously, the surgical measures were quite inadequate. He cured the patients by orthoptic therapy and (to me this is more important) by adequate surgical means. The point which I wish to bring out, however, is that one should recognize this condition and give adequate surgical treatment prior to the age of 5 years, and that if operation is not done prior to this age, and the patient given the chance to learn suppression, or at least to restore a fovea-to-fovea relation, one should recognize the condition when it arises, which it will at about the age of 7 or 8 years, with the complaint of diplopia. One then should carry out orthoptic treatment and adequate surgical measures. I should like to ask Dr. Swan the average age of the patients in the present series and the age of the youngest patient in the series.

Dr. Hermann N. Burian, Boston: The excellent paper which Dr. Swan has presented demonstrates again the fruitfulness of the physiologic approach to problems of ocular motility. The paper invites discussion from two pionts of view: (1) the facts and observations and (2) the interpretation of the facts. As a report of facts and observations it is outstanding for accuracy. This is in contrast to many papers on strabismus, in which the data leave much to be desired with respect to both accuracy and completeness. As an interpretation of the results, as to how the peculiar position of the blindspot influences the clinical features, course and treatment, there is room for discussion.

One may assume the case of a young child who is hypermetropic and who accommodates and overconverges in order to see clearly. If the child acquires strabismus, he will also experience diplopia. Heretofore, two ways have been known in which the child can rid himself of the diplopia: He may learn to suppress the unwanted image, or he may learn to localize the unwanted image in the more or less close vicinity of the fixated object; he may develop what is known as anomalous correspondence. Dr. Swan has shown us that there is a third way of alleviating diplopia. If the angle of squint, the hypermetropia and all other etiologic factors are such that the blindspot covers the object of regard, the visual problems of the child are solved; he does not have to look for further adjustments.

In cases in which this blindspot syndrome has existed since infancy or early childhood, the interpretation of the other clinical features offers no problem. These features are the absence of suppression scotomas in the binocular field of vision, normal retinal correspondence and a fair degree of binocular cooperation and an excellent functional result following properly conducted treatment.

One would not expect patients who have always had the blindspot syndrome to suppress or develop anomalous correspondence; there is no call for it. Also explained is the remarkable percentage of functional cures in cases of this syndrome. If therapeutic measures succeed in eliminating the deviation, all that is left is to start the patient on the road to normal binocular vision. Surely, cases of this type will be relatively rare, for special conditions are required, one of them being great stability of the angle of squint. According to Dr. Swan, there is a sizable number of patients who originally had a larger angle of squint and who acquired the blindspot syndrome when the angle decreased, either spontaneously or owing to therapeutic measures. In these patients, in whom the blindspot began to overlie the object of regard at a relatively late date, this course could not explain the prevalence of normal retinal correspondence and the absence of suppression scotomas. One must assume that these features existed prior to the acquisition of the blindspot syndrome. Otherwise one would have to expect at least some of these patients to show anomalous correspondence and suppression scotoma. While it is not possible to see what connection there could be between the blindspot and the other clinical features in these cases, I believe that these features are explained by assuming that the patients always had normal correspondence and little suppression. It is recognized that there are cases of esotropia with normal correspondence. For the establishment of anomalous correspondence, a number of factors are necessary. One such factor is a certain plasticity of the sensory apparatus of the eye. Some patients suppress more readily than others; some develop anomalous correspondence more readily than others. Both processes are closely connected. In general, patients with normal correspondence are more apt to complain of diplopia than patients with anomalous correspondence. Such patients would obviously be greatly benefited if they could keep their angle of squint within such limits that the image of the object of attention would always fall on the blindspot. Since suppression and anomalous correspondence go together, suppression scotomas are much more frequently found in anomalous than in normal correspondence. Also, they are larger the less stable the angle of squint is. The patient described by

Dr. Swan had, as he stresses, a stable angle of squint, and all the patients had normal correspondence. These factors, rather than the position of the blindspot, would seem to account for the absence of suppression scotomas. Dr. Swan has by definition excluded from his consideration patients in whom the blindspot forms part of a suppression scotoma. This may seem arbitrary, but these patients should, indeed, present a different behavior. I should like to ask Dr. Swan whether I am correct in assuming that the latter patients generally tended to have anomalous correspondence.

The selection which Dr. Swan has made also accounts for the ease with which diplopia is elicited by means of prisms in the patients with the blindspot syndrome. Dr. Swan emphasizes that diplopia can be elicited in the cases under discussion when the image of the fixation point is displaced from the blindspot in the deviated eye. He considers this a sure sign that the blindspot plays an essential part in alleviating the diplopia. If diplopia cannot be elicited in this way, he does not recognize the case as falling into the category of the blindspot syndrome.

In my experience, the cases of strabismus in which diplopia cannot be elicited by means of prisms are extremely rare. But it is much more difficult to do so in patients with anomalous than in patients with normal correspondence. It is to be expected that the patients included in Dr. Swan's group should readily report diplopia when the image of the fixation point is brought from the blindspot on an adjacent retinal area.

In it particularly difficult to correlate the last two common features of the cases, namely, the fair binocular cooperation, either from the start or after brief orthoptic treatment, and the amazingly good result with appropriate treatment, with the position of the blindspot. These features, too, seem to be inherent in the case and connected with the normal correspondence, rather than with the particular angle of squint.

The course of treatment suggested by Dr. Swan in these cases does not seem to be essentially different from that recommended in all cases of esotropia, but the results achieved are certainly far superior to those in the general run of cases. I should like to ask Dr. Swan whether he could quote for us comparative figures from his large experience with cases of esotropia of all types.

After studying the evidence which Dr. Swan has so ably presented to us, there still remains in my mind the question of the actual functional significance of the blindspot in cases of this condition. There is no doubt about the role of the blindspot in alleviating the diplopia when the angle of squint is such that the blindspot overlies the object of regard. But the other features of the cases are not explained by this position of the blindspot, and therefore I do not believe that one should give it such prominence as to speak of a "blindspot syndrome." It would seem to me better to state that Dr. Swan has selected a group of esotropic patients with normal correspondence, fair binocular cooperation and an excellent prognosis in whom the angle of squint is such that they are enabled to make use of the blindspot provided by nature to rid themselves of diplopia.

DR. KENNETH C. SWAN, Portland, Ore.: I am delighted with the discussion, for Dr. Adler and Dr. Burian have not only brought up some of the problems which my colleagues and I have considered but have introduced fresh aspects of the question.

I agree with Dr. Adler that the blindspot syndrome is usually associated with the so-called accommodational types of squint when it develops spontaneously. I appreciate his endorsement of our statement that inadequate treatment is of no avail.

I cannot state the average age of our patients, but the oldest patient in whom we have observed the syndrome is now 47. Determination of the youngest patient to develop the condition is limited not by the actual onset of the syndrome but by one's inability to recognize it; one cannot be certain of the diagnosis without subjective tests. We have been able to make these tests on some intelligent children 3 or 4 years of age.

Dr. Burian suggested several interesting points in the relation of normal correspondence to the presence of the blindspot in the central position. He also raised the question of the role of the blindspot in other conditions. During the eight year period in which we have been studying these cases, we have extended investigation of the field of binocular vision into other types of cases than those presented but have found it a field so large as to be beyond the scope of a single group of investigators. I make the plea that the study of the field of binocular vision be used in the routine examination of patients with esotropia. It is a visual test which is of great clinical importance, both in prognosis and in treatment; yet it is little used. It is simple to study the field of binocular vision of an intelligent youngster with the Lancaster red-green test or with similar filter–twin projector systems.

With respect to our good results, there should be some explanation. We have been persistent in treatment of these patients, and we have followed the results of treatment with the thoroughness required of a research problem. The average period of treatment for the cured patients was seventeen months, and the paper in no way reflects the extensive efforts expended in the training and observation of these patients by the orthoptic technicians and our staff.

Dr. Burian has made a good point in questioning whether the blindspot syndrome is a clearcut entity. We have designated the condition in this series of cases by this name primarily for the purpose of calling the attention of other ophthalmologists to the mechanism for purposes of study; however, it occurred to me, after hearing Dr. Burian's excellent discussion, that we should perhaps speak of "the blindspot mechanism," rather than limit ourselves to a single group of cases by using the term "the blindspot syndrome."

USE OF ROENTGEN THERAPY FOR RETINAL DISEASES CHARACTERIZED BY NEW-FORMED BLOOD VESSELS

(Eales's Disease; Retinitis Proliferans)

A Preliminary Report

JACK S. GUYTON, M.D.
BALTIMORE
AND
ALGERNON B. REESE, M.D.
NEW YORK

DURING the past eighteen months we have given intensive roentgen therapy to the posterior ocular segment in a series of patients with ocular diseases characterized by retinal and vitreous hemorrhages, with secondary fibrous tissue formation and with new-formed blood vessels extending into the vitreous. A total of 22 eyes in 14 patients have been so treated. The ocular disease was classified as typical Eales's disease in 8 of these patients, as atypical Eales's disease in 4 patients and as diabetic retinitis proliferans in 2 patients. The roentgen therapy has given sufficiently encouraging immediate results to warrant a preliminary report.

TECHNIC OF ROENTGEN THERAPY

The irradiation technic devised by Martin and Reese [1] for the treatment of retinoblastoma was utilized to give large doses of roentgen radiation to the posterior ocular segment with minimal effects on the vulnerable anterior segment. The cones and portals employed were

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From the Wilmer Ophthalmological Institute of the Johns Hopkins Medical School, Baltimore, and the Institute of Ophthalmology of the Presbyterian Hospital and the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York.

1. Martin, H. E., and Reese, A. B.: Treatment of Retinal Gliomas by the Fractionated or Divided Dose Principle of Roentgen Radiation, Arch. Ophth. **16**: 733-761 (Nov.) 1936; Treatment of Retinoblastoma (Retinal Glioma) Surgically and by Irradiation, ibid. **27**:40-72 (Jan.) 1942; Treatment of Bilateral Retinoblastoma (Retinal Glioma) Surgically and by Irradiation, ibid. **33**:429-439 (June) 1945.

the same as those used in the cases of retinoblastoma (cylinders 2.5 cm. in diameter, shaped to fit the lateral orbital margin and the base of the nose). The following factors were employed: 250 kilovolts; filter, 1.5 mm. copper; half-value layer, 1.9 mm. copper; target-skin distance, 60 cm. ; 30 milliamperes; portal size, 2.5 cm. The dosage was varied considerably, inasmuch as the exact nature of the diseases and the response to high voltage roentgen therapy were not known. The first patients treated received 400 r (in air) three times a week, the temporal portal being utilized more frequently than the nasal. The nasal portal was later eliminated because the presence of the fellow eye hinders its proper application, whereas in the cases of retinoblastoma the fellow eye has always been enucleated. Also, if the nasal portals are used for treatment of both eyes, the cross fire through the bridge of the nose gives a double dose to this area, which might produce necrosis. In the original cases 8,000 to 10,000 r was given through the temporal portal and 5,000 to 6,000 r through the nasal one, but in the later cases this was reduced to a total of 3,500 to 6,000 r, given only through the temporal portal. Erythema of the skin appeared after approximately 1,000 to 1,500 r had been given to a field and became brisker as the dose went higher. No ulceration or serious complications have arisen. The skin healed rapidly after treatment was discontinued, but late changes due to radiation (some atrophy and pigmentation of the skin) occurred in some patients. If the total dose did not exceed 6,000 r, the patients could tolerate 500 r three times a week through the temporal portal alone, thus shortening the treatment time. The eyes of all patients treated were examined before and at frequent intervals during and after the radiation therapy.

PLATE I

Fig. 1 (case 1; Nov. 28, 1944).—Right eye four months preceding roentgen therapy.

Fig. 2 (case 1; March 20, 1945).—Right eye shortly before roentgen therapy, showing extension of vessels into anterior vitreous.

Fig. 3 (case 1; May 25, 1945).—Right eye after receiving 8,000 r, showing marked regression of vessels.

Fig. 4 (case 1; July 13, 1945).—Right eye after receiving entire course of 13,000 r, showing complete disappearance of new-formed vessels.

Fig. 5 (case 1; March 20, 1945).—Left eye two months preceding roentgen therapy.

Fig. 6 (case 1; May 25, 1945).—Left eye immediately preceding roentgen therapy, showing extension of vessels into anterior vitreous.

Fig. 1

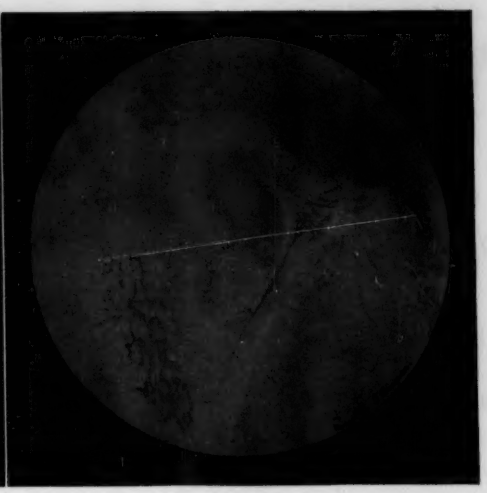

Fig. 2

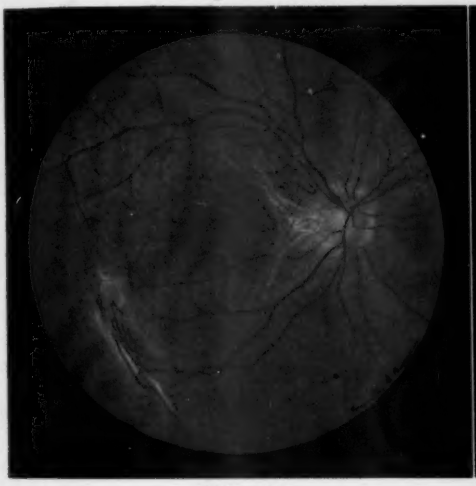

Fig. 3

Fig. 4

Fig. 5

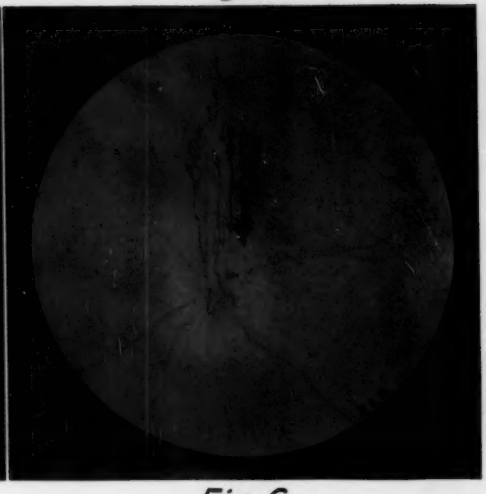

Fig. 6

PLATE I

PLATE II

Fig. 7 (case 1; July 13, 1945).—Left eye after receiving 7,200 r, showing marked regression of vessels.

Fig. 10 (case 4; Aug. 10, 1945).—Right eye immediately preceding roentgen therapy.

Fig. 11 (case 4; Dec. 7, 1945).—Right eye after completion of therapy (15,000 r), showing complete collapse of new-formed vessels but persistence of tiny aneurysmal dilatations in lower temporal retinal venules.

Fig. 14 (case 5; July 10, 1946).—Left eye after end of first course of therapy (4,000 r), showing area of probable healed chorioretinitis and occlusion of terminal retinal vein, with two small fresh hemorrhages.

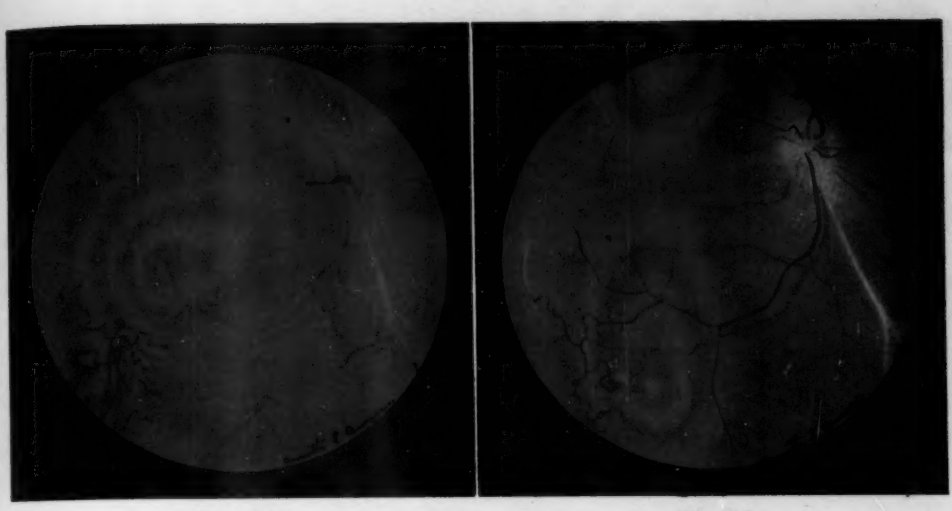

Fig. 10 Fig. 11

Fig. 7

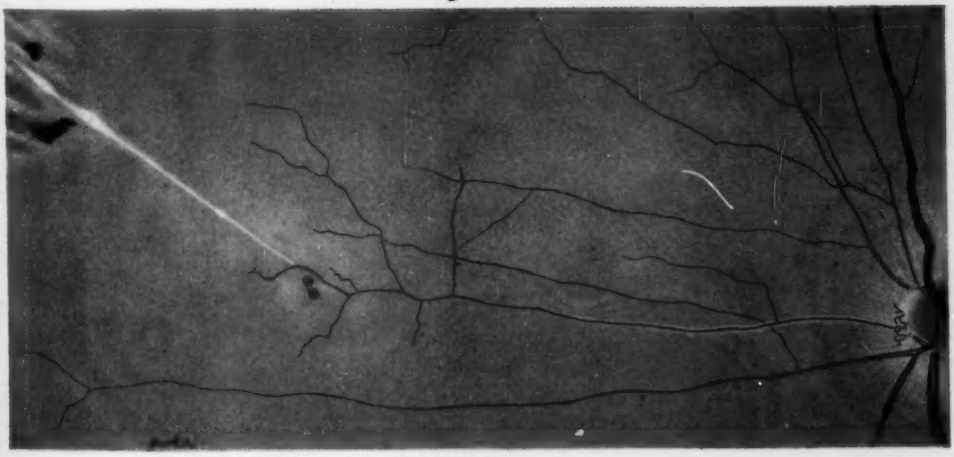

Fig. 14

PLATE II

REPORT OF CASES

The 14 cases in this series are summarized in the accompanying table. Certain aspects of these cases are also described briefly.

TYPICAL EALES'S DISEASE

CASE 1.—W. G., a white man aged 37, had a number of small recurrent hemorrhages with rapid proliferation of blood vessels in the vitreous of each eye. There was no apparent uveitis. During four months' observation without roentgen therapy, there were additional fresh hemorrhages in each eye with extension of new-formed vessels into the anterior portion of the vitreous, and at least one of the fresh hemorrhages in the vitreous of the right eye appeared to come directly from one of these new vessels. There was a questionable relationship of several of these recurrent hemorrhages to injections of tuberculin. The right eye was then treated with roentgen radiation (total dose, 13,000 r). There were no further vitreous hemorrhages in this eye, and the new-formed vessels disappeared with amazing rapidity (plate I, figs. 1 to 4). In the untreated (left) eye there were four additional recurrent hemorrhages and considerable progression of new-formed vessels during the succeeding two months. We no longer felt justified in withholding roentgen irradiation to the left eye, and the effect of therapy (total dose, 14,000 r) was similar to that in the right eye (plate I, figs. 5 and 6, and plate II, fig. 7). Subsequently, a patch of healed choroiditis could be seen in the far lower periphery of the left eye, but there was no definite choroiditis in the right eye. There has been no recurrence of either hemorrhages or formation of new vessels in the eighteen months since the eyes were treated. The patient was sensitive to 0.001 mg. of old tuberculin given intracutaneously.

CASE 2.—In B. deE., a white man aged 40, anterior uveitis developed in both eyes in March 1944. The uveitis subsided within several weeks, but massive vitreous hemorrhages developed in the right eye in August 1944 and in the left eye in February 1945. On July 3, 1945, he was found to have extensive retinitis proliferans with an abundance of new-formed vessels and partial retinal detachment in the right eye. In the left eye there was only a faint red reflex. Roentgen therapy was given both eyes (total doses, 12,000 r for the right eye and 10,000 r for the left eye). The new-formed vessels in the vitreous of the right eye thereupon disappeared completely, and there was considerable regression of the fibrous bands extending into the vitreous and of the retinal detachment. The left fundus still could not be seen when last examined (Sept. 15, 1946). The patient was sensitive to 0.001 mg. of old tuberculin given intracutaneously.

CASE 3.—S. M., a white woman aged 24, had recurrent retinal and vitreous hemorrhages for two years before she was first examined, on Jan. 6, 1944. Glaucoma had developed in the right eye ten days previously, with new-formed vessels on the anterior surface of the iris. This eye was enucleated, and examination showed in the posterior segment retinal and vitreous hemorrhages with fibrous tissue and new-formed vessels extending from the retina into the vitreous (fig. 8). The vitreous contained serous exudate, as well as actual hemorrhage. There were an inflammatory occlusion of the retinal veins and arteries and a peculiar thickening of the internal limiting membrane, but the inflammatory response was nonspecific (fig. 9). The left eye showed considerable fibrous tissue and new vessel formation extending into the vitreous and extreme retinal perivascular sheathing. Vision in her left eye gradually failed until June 1945, when she was given roentgen radiation, in a total dose of 15,000 r, to that eye. The new

Diagnostic Classification	Case No.	Age, Yr.	Sex	Eye	Condition Preceding Roentgen Therapy: Vision with Correction*	Duration of Symptoms	History of Vitreous Hemorrhages	New-Formed Vessels in Vitreous	Fibrosis Extending Into Vitreous	Retinal Detachment
Typical Eales's disease	1	37	M	R	20/15 —1	10 mo.	6 small	++++	±	–
				L	20/15 —2	12 mo.	13 small	++++	±	–
	2	40	M	R	20/70	11 mo.	1 massive; ? others	+++	+++	++
				L	1/200	6 mo.	1 massive; ? others	Faint	Red reflex	
	3	24	F	R	NLP	2 yr.	Several small	++++	+++	+
				L	20/100 +1	2 yr.	Several small	++++	+++	+
	4	30	M	R	20/20 —3	5 yr.	2 moderate	+++	++	–
				L	LP	5 yr.	1 small and 1 massive	—	Red reflex	
	5	29	M	R	3/200	7 mo.	Many small	+++	++++	+
				L	20/15	5 mo.	Many small	++	+	–
	6	26	M	R	20/400	17 mo.	Many moderate	?	++	++
				L	20/200	20 mo.	Many moderate	?	++	++
	7	37	F	R	20/70	1½ mo.	Many small	+++	+++	++
				L	1/200	5 mo.	Many small	+++	++++	++++
	8	46	M	R	HM	2 yr.	10+ small	?	++++	?
				L	HM	6 yr.	20+ small	?	++++	?
Atypical Eales's disease	9	25	F	R	20/100	1 mo.	Questionable	+++	+++	–
				L	20/15	....	0	—	—	–
	10	40	M	R	20/15	5 yr.	2 medium	+	+	–
				L	5/200	....	0	—	—	–
	11	42	M	R	20/70 +1	6 mo.	10 small	—	+	–
				L	20/20 —1	14 mo.	20 small	—	—	–
	12	34	F	R	NLP	9 yr.	Many	—	Red reflex	
				L	LP	9 yr.	Many	±	+	±
Diabetic retinitis proliferans	13	53	F	R	20/40	3 yr.	Questionable	++	*++	–
				L	20/40	3 yr.	0	—	—	–
	14	42	M	R	20/200	1 yr.	Questionable	++	±	–
				L	20/200	1 yr.	Questionable	+++	+++	–

* NLP indicates no light projection; LP, light projection, and HM, hand movements.

Other Comment	Roentgen Therapy (r in Air)			Follow-Up Period	Results				
	Temporal Portal	Nasal Portal	Total		Final Vision*	Subsequent Vitreous Hemorrhages	Diminution in New-Formed Vessels	Diminution in Fibrosis	Other Comment
...vident uveitis	8,000	5,000	13,000	18 mo.	20/15	—	Complete	Marked	.....
...vident uveitis	8,000	6,000	14,000	16 mo.	20/15	—	Complete	Marked	Visible area of healed choroiditis
...erior uveitis 5 mo. before vitreous hemorrhages	7,000	5,000	12,000	14 mo.	20/25	—	Complete	Moderate	Retinal detachment less
...erior uveitis 11 mo. before vitreous hemorrhages	5,000	5,000	10,000	14 mo.	LP	—	Still only faint red reflex		.....
...ciation because of absolute glaucoma with new-formed vessels on iris	Sections of posterior segment showed retinitis proliferans, nonspecific inflammatory occlusion of retinal vessels and peculiar thickening of internal limiting membrane								
...rene periarterial streaking throughout fundus; irregular dilation and beading of retinal veins	10,000	5,000	15,000	14 mo.	20/30	—	Complete	Marked	.....
...vident uveitis	10,000	5,000	15,000	12 mo.	20/20 —2	—	Complete	Slight	.....
...or light projection; roentgen radiation therapy not believed justifiable	.....	.....	.....	....	.....	..	.....	.....	.....
...vident uveitis	2,500	1,000	3,500	4 mo.	5/200	—	Moderate	None	.....
...rked streaking along one artery, leading to area of possible chorioretinitis	2,500	1,500	4,000	4 mo.	20/15	1 small	Moderate	Questionable	Given 2,000 r additional radiation after small recurrent retinal hemorrhage
...hite chorioretinitis noted in army while hemorrhages were developing	4,000	.....	4,000	3 mo.	20/200	—	?	?	Fundus not seen well enough preceding radiation to permit tabulation of changes
...vident uveitis	4,000	.....	4,000	3 mo.	20/25	—	?	?	Fundus not seen well enough preceding radiation to permit accurate tabulation of changes
...vident uveitis	2,000	2,000	4,000	5 mo.	20/40	—	Moderate	Slight	Retinal detachment only slightly less
...vident uveitis	2,000	2,000	4,000	5 mo.	3/200	—	Moderate	Slight	Retinal detachment still ++++
...o much vitreous hemorrhage for anything to be seen except marked fibrosis in vitreous	4,000	.....	4,000	2 mo.	2/200	—	?	?	Still too much vitreous hemorrhage for details to be seen with ophthalmoscope
...o much vitreous hemorrhage for anything to be seen except marked fibrosis in vitreous	4,000	.....	4,000	2 mo.	2/200	—	?	?	Still too much vitreous hemorrhage for details to be seen with ophthalmoscope
...veral retinal veins partially occluded; diabetes for 18 mo., but no diabetic retinopathy	4,000	.....	4,000	5 mo.	20/200	—	Moderate	Questionable	.....
...rmal except that veins appeared large	.....	.....	.....	....	.....	..	.....	.....	.....
...latation of venules in temporal periphery; retinal hemorrhages only in region supplied by a branch of superior temporal vein; white serous exudate in lower vitreous	3,000	3,000	6,000	8 mo.	20/15	2 small	Complete	Questionable	Venules less dilated but not completely obliterated; white serous exudate in lower vitreous partly absorbed; small fresh hemorrhages and cotton-wool exudates around disk
...mblyopia ex anopsia from anisometropia; eye otherwise normal	.....	.....	.....	....	.....	..	.....	.....	.....
...trabismus with partial amblyopia in right eye; both eyes showed some irregular dilatation in retinal venules; organization of retinal hemorrhages and, in vitreous of left eye, some white serous exudate	4,000	.....	4,000	3 wk.	Insufficient follow-up period for judgment of results				.....
...ondition same as above	4,000	.....	4,000	3 wk.	Insufficient follow-up period for judgment of results				.....
...ighthous uveitis with recurrent attacks	.....	.....	.....	....	.....	..	.....	.....	.....
...ighthous uveitis with recurrent attacks	1,800	1,700	3,500	1 mo.	LP	—	Questionable	Questionable	Retinal degeneration and optic atrophy
...evere diabetic retinopathy	2,000	2,000	4,000	5 mo.	20/50	—	Complete	Slight	Retinal hemorrhages continued to appear
...iabetic retinopathy only—no new-formed vessels	.....	.....	.....	....	.....	..	.....	.....	.....
...evere diabetic retinopathy	4,000	.....	4,000	6 mo.	.....	+	Marked	Questionable	Initial improvement but fresh vitreous
...evere diabetic retinopathy	4,000	.....	4,000	6 mo.	.....	+	Marked	Questionable	Hemorrhages on last examination

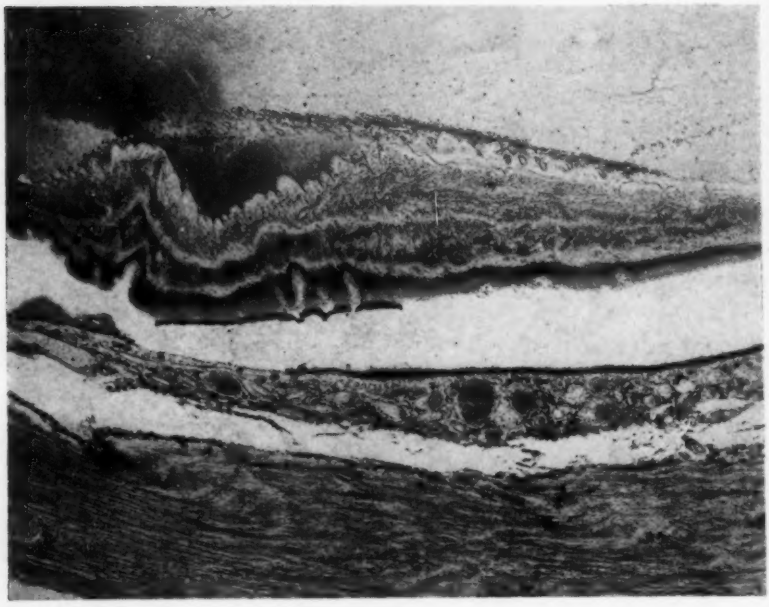

Fig. 8 (case 3).—Photomicrograph from posterior segment of right eye, showing new-formed vessels and fibrous tissue extending from retina into vitreous hemorrhage.

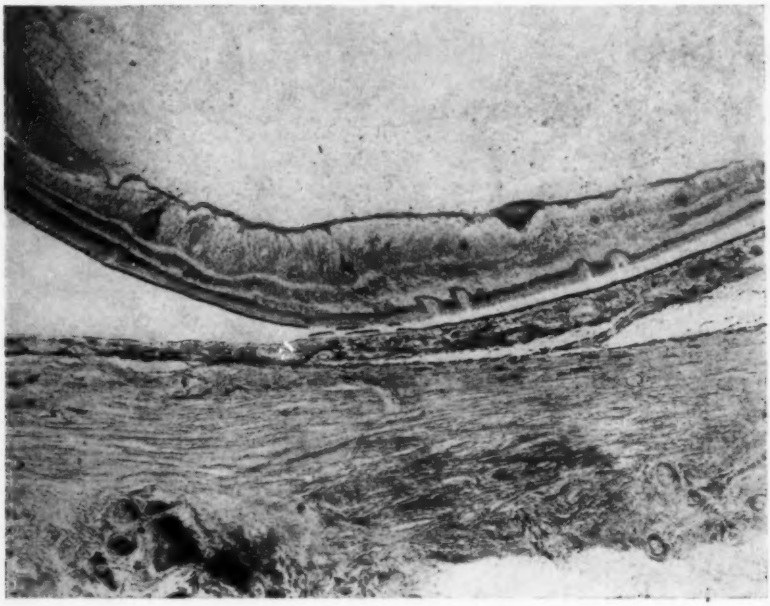

Fig. 9 (case 3).—Photomicrograph from posterior segment of right eye, showing retinal perivascular inflammation, inflammatory occlusion of retinal veins and peculiar thickening of internal limiting membrane.

vessels disappeared, and there have been no fresh hemorrhages during the fourteen months she has been followed since the irradiation; but there are still many fine dilatations and tortuosities of the retinal venules, and the perivascular streaking is unchanged. There was never any apparent uveitis in either eye. A patch test gave a negative reaction to a 1:10,000 dilution of old tuberculin U. S. P. At one time she had eosinophilia, with a count of from 6 to 8 per cent eosinophils, and a 2 plus reaction to the cephalin flocculation test; but all other examinations, including determination of the sedimentation rate, complete blood studies and muscle biopsy, gave normal results.

CASE 4.—P. M., a white man aged 30, had a history of at least two distinct vitreous hemorrhages in each eye during the preceding five years. Examination (Aug. 10, 1945) of the right eye showed a little blood scattered through the lower part of the vitreous, with new-formed vessels extending far into the vitreous in three areas and small aneurysmal dilatations in the new vessels in the lower temporal part of the vitreous (plate II, fig. 10). There was a small, apparently fresh vitreous hemorrhage, which appeared to come from one of the new-formed vessels in the anterior portion of the vitreous (not shown in the illustration). The left eye had poor light projection and no red reflex. The right eye was given roentgen therapy (total dose, 15,000 r). The new-formed vessels disappeared completely, but a few tiny aneurysmal dilatations of retinal venules remained in the lower temporal quadrant of the retina (plate II, fig. 11). There has been no recurrence of hemorrhages or of formation of vessels during the year since he was treated. There was never any apparent uveitis in either eye. The patient was sensitive to 0.001 mg. of old tuberculin U. S. P. given intracutaneously, and biopsy of a cervical lymph node showed actual tubercle bacilli.

CASE 5.—R. B., a white man aged 29, began to have many small recurrent retinal and vitreous hemorrhages in the right eye during July 1945, and in the left eye two months later. Examination on Feb. 13, 1946 showed extensive fibrosis and new vessel formation in the vitreous of the right eye, with partial retinal detachment. In the left eye there were scattered hemorrhages in the temporal part of the retina and the vitreous, with aneurysmal dilatations of some retinal venules in this area, an area of retinal hemorrhage with obliteration of a terminal arteriole in the nasal periphery and a sheet of new-formed vessels extending into the vitreous from the nasal side of the disk (fig. 12). There was no evidence whatever of any vitreous or retinal hemorrhage close to the area of retinitis proliferans, which extended forward from the disk. Roentgen therapy was given in a total dose of 3,500 r to the right eye and of 4,000 r to the left eye. There was partial collapse of the new-formed vessels in each eye, only the larger trunks remaining patent, but little or no decrease in fibrosis (fig. 13). On July 1, 1946, the patient had symptoms of another hemorrhage in the left eye and was found to have two small retinal hemorrhages with a faint diffuse haze in the vitreous (plate II, fig. 14). He was given an additional 2,000 r to the left eye, and has not been reexamined since the course was completed. The indistinct scar in the nasal periphery of the left eye was the only evidence of probable uveitis in either eye. He was sensitive to 0.001 mg. of old tuberculin, given intracutaneously.

CASE 6.—R. R., a white man aged 26, began having recurrent retinal and vitreous hemorrhages in both eyes eighteen months before he was examined, and six months before examination he was said to have shown "organization" of hemorrhages, with an area of chorioretinitis in the right eye but no uveitis in the left eye. He was said to have given a positive reaction to tuberculin (dilution

Fig. 12 (case 5; Feb. 13, 1946).—Left eye immediately preceding roentgen therapy.

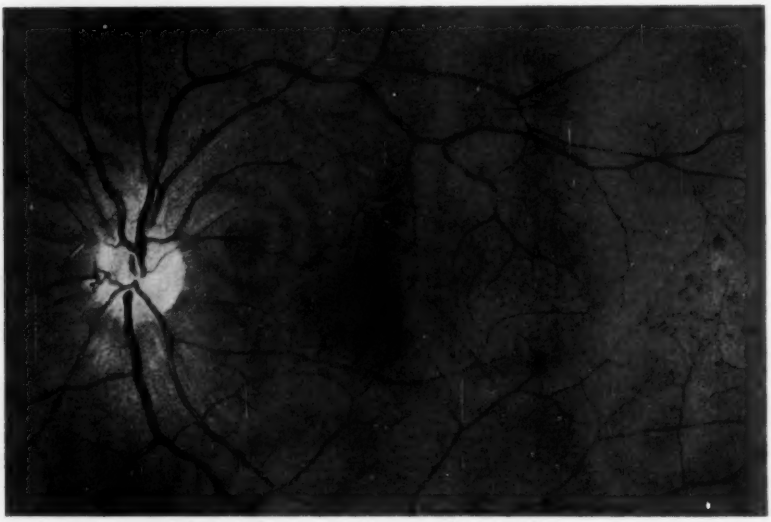

Fig. 13 (case 5; June 5, 1946).—Left eye after conclusion of first course of therapy (4,000 r), showing partial collapse of new-formed vessels and persistence of aneurysmal dilatations of retinal venules in temporal periphery.

not known). On March 1, 1946, the vitreous of each eye contained so much blood that nothing could be determined ophthalmoscopically except that there was retinitis proliferans with partial retinal detachment in each eye. Roentgen therapy (4,000 r to each eye) was followed by gradual clearing of the vitreous in each eye. Three months later vision had improved from 20/200 to 20/25 in the left eye, and the fundus could be seen fairly well, showing partial retinal detachment still present, with moderate fibrosis on the surface of the retina but no new-formed vessels. The right fundus still could not be seen plainly.

CASE 7.—O. St. J., a white woman aged 37, had many small recurrent vitreous hemorrhages in her left eye during November 1945, and a similar hemorrhage in her right eye on Feb. 1, 1946. Examination March 15, 1946 showed small patches of blood in the vitreous of the right eye and extensive retinitis proliferans with many new-formed vessels and partial retinal detachment (fig. 15). The left eye showed a similar, but more advanced, picture, there being massive retinitis prolifer-

Fig. 15 (case 7; March 26, 1946).—Right eye immediately preceding roentgen therapy.

ans with complete retinal detachment. Roentgen therapy was given in a total dose of 4,000 r to each eye. The smaller new-formed vessels in both eyes completely disappeared but the larger ones only shrank in size, remaining patent (fig. 16). There were some decreases in fibrosis of the vitreous and some flattening of the right retina, but the left retina remained completely detached. There has been no recurrence of hemorrhages or of new vessel formation during the five months of observation since the roentgen therapy. There was never any apparent uveitis. The patient had a negative reaction to 1 mg. of old tuberculin given intracutaneously but showed involvement of the hilar nodes in roentgenograms of the chest.

CASE 8.—G. P., a white man aged 46, had had at least twenty vitreous hemorrhages in his left eye during the preceding six years and at least ten in his right eye during the preceding two years. Examination on July 10, 1946 showed considerable unabsorbed blood in each vitreous. Details of the fundus could not be

seen except that massive retinitis proliferans was dimly visible in each eye. Roentgen therapy was then given, 4,000 r to each eye. At the time of writing, the vitreous is slowly clearing in each eye, but details of the fundus are still not clearly visible. There has been no apparent uveitis. He has shown a positive reaction to 0.001 mg. of old tuberculin U. S. P. given intracutaneously and has a healed tuberculous lesion in the apex of his left lung.

ATYPICAL EALES'S DISEASE

CASE 9.—B. G., a white woman aged 25, had numerous retinal and questionable vitreous hemorrhages in her right eye in January 1946. Examination on Feb. 19, 1946 showed marked fibrosis with new vessel formation on the retina and extending slightly into the vitreous of that eye. There was apparent partial occlusion of several of the retinal veins. The left eye was normal except for unusually large veins. The patient received 4,000 r to the right eye, beginning April 13, 1946.

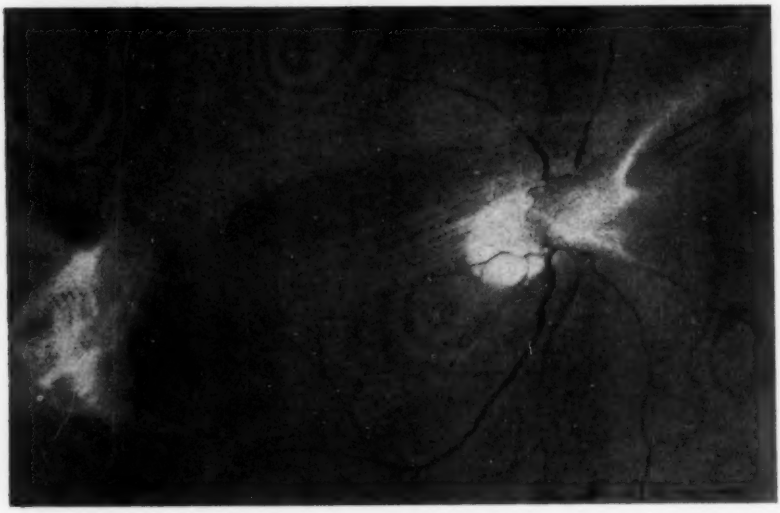

Fig. 16 (case 7; July 31, 1946).—Right eye three months after completion of therapy (4,000 r), showing partial collapse of new-formed vessels.

The new-formed vessels partially disappeared, and there have been no additional hemorrhages in the five months since the eye was treated. She had diabetes for eighteen months preceding therapy but no diabetic retinopathy. She had no apparent uveitis, and sensitivity to tuberculin was not determined.

CASE 10.—A. H., a white man aged 40, had a history of a massive retinal and vitreous hemorrhage in his right eye while lifting a heavy weight five years previously. The vitreous hemorrhage had cleared quickly, and a photograph of the fundus taken one month later (fig. 17) showed an extensive retinal hemorrhage along the lower branch of the superior temporal vein, occurring distal to a point where this vein coiled in corkscrew fashion around the superior temporal artery. The retinal hemorrhage had gradually cleared, with some fibrosis; and the patient had had no further symptoms until a second large hemorrhage occurred on Dec. 1, 1945, this time spontaneously. Examination on December 18 showed that the left eye was normal except for amblyopia ex anopsia. In the right eye there was a massive

retinal and a slight vitreous hemorrhage along the distribution of the lower branch of the superior temporal vein, a small branch of which was obliterated, with some organization of the hemorrhage (including new-formed vessels) in places. There was also white serous exudate in the lower portion of the vitreous. Throughout the involved area of the retina, but extending also into areas supplied by the lower temporal vein, there were corkscrew irregularities and tiny aneurysmal dilatations of the fine retinal venules (fig. 18). These small varicosities were still present after roentgen therapy (6,000 r) but were less pronounced than before treatment (fig. 19). There was slight decrease in fibrosis following roentgen therapy, and the new-formed vessels disappeared. He had symptoms of two small hemorrhages during June 1946, and examination on October 1 showed several tiny retinal hemorrhages and cotton-wool exudates scattered about the posterior portion of the fundus, partial absorption of the serous exudate in the lower part of the vitreous and a peculiar localized plexus of dilated capillaries at one point along the remaining branch of the originally involved vein (fig. 20). He is now receiving

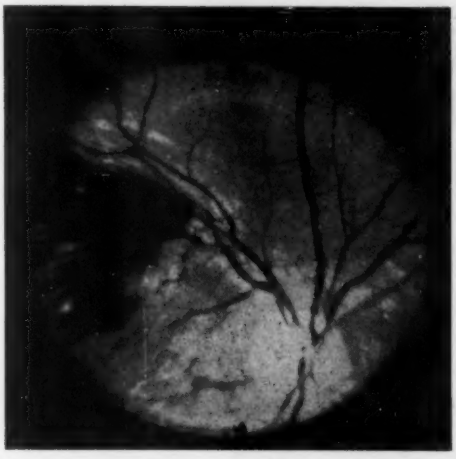

Fig. 17 (case 10; February 1941).—Right eye one month after first hemorrhage, showing corkscrew anomaly in lower branch of superior temporal vein.

3,000 r of additional roentgen radiation. There was never any evidence of uveitis. He was sensitive to 0.001 mg. of old tuberculin U. S. P. given intracutaneously.

Case 11.—L. P., a white man aged 42, had had numerous retinal and small vitreous hemorrhages in the left eye during the preceding fourteen months and in the right eye during the preceding six months. He had had subjective exacerbations in both eyes approximately forty-eight hours after each of three intracutaneous injections of tuberculin. Examination of the right eye on July 19, 1946 showed slight vitreous hemorrhage and a peripheral medium-sized retinal hemorrhage with early organization, with dilatation of a retinal vein just at the site of its emergence from the area of hemorrhage. In the left eye there were more vitreous hemorrhages and clumps of white serous exudate in the lower portion of the vitreous, with streaks of retinal hemorrhage undergoing absorption, but without organization, in the temporal periphery. A retinal vein supplying the latter area had two short stretches of doubling of the channel at one place, with a trace of adjacent absorbing retinal hemorrhage, suggesting occlusion and recanalization of the vein at this point. There was also a small aneurysmal dilatation at one

point in a branch of the superior nasal vein, but no adjacent hemorrhage A total of 4,000 r was given each eye. The patient has not been examined since the conclusion of this therapy (Aug. 10, 1946).

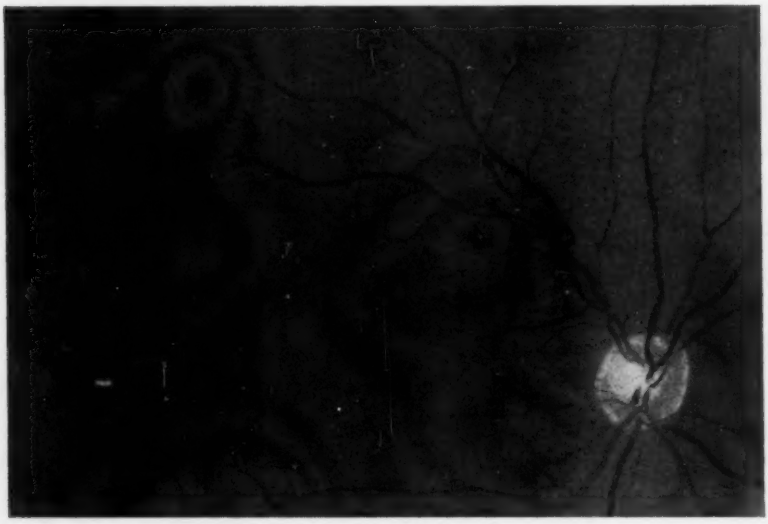

Fig. 18 (case 10; Dec. 18, 1945).—Right eye immediately preceding roentgen therapy. Note the varicosities and tiny aneurysmal dilatations in terminal venules of lower temporal vein, as well as of upper vein.

Fig. 19 (case 10; Feb. 12, 1946).—Right eye after completion of therapy (6,000 r), showing regression of new-formed vessels but some persistence of varicosities in retinal venules.

Case 12.—S. A., a white woman aged 34, with a history of many hemorrhages in the vitreous of both eyes during the preceding six years, was first examined March

5, 1943. The right eye was blind, with evidence of healed anterior uveitis and a dense complicated cataract. The left eye showed a normal anterior segment, some vitreous hemorrhage and scattered retinal hemorrhages with fibrosis. Vision in the left eye was 20/70 at that time. During the next three years she had several recurrent vitreous hemorrhages in the left eye, and on June 9, 1946 there developed acute anterior uveitis with a large hypopyon (containing some hemorrhage) and temporary loss of light perception. The anterior uveitis cleared within a few days, and she was found to have moderate vitreous hemorrhage. Roentgen radiation (3,500 r) was given to the left eye. The vitreous hemorrhage gradually cleared within a month, and she was then seen to have indistinct white areas (apparently a mixture of atrophy and of fibrosis) scattered throughout the retina, with a pale disk and vision still limited to light perception. She had aphthous lesions of the mucous membranes, deficiency of plasma ascorbic acid, slightly increased capillary fragility, a probable tuberculous infection of one kidney and sensitivity to 0.001 mg. of old tuberculin given intracutaneously.

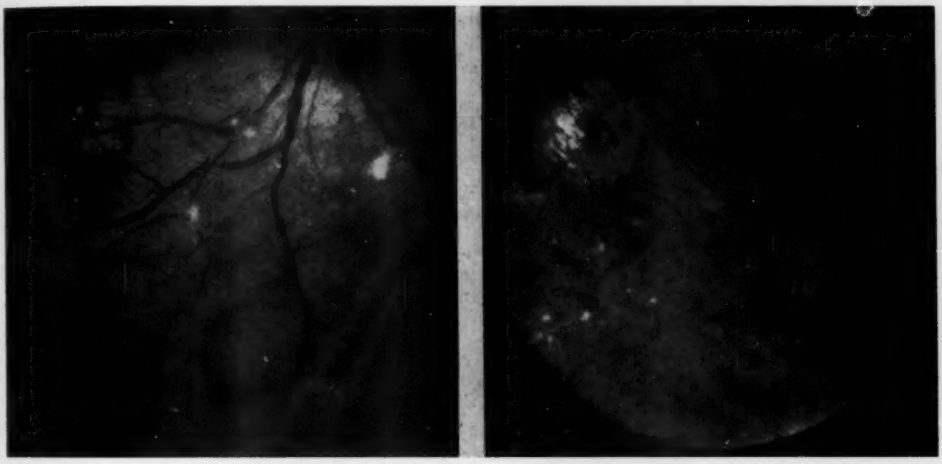

Fig. 20 (case 10).—Right eye seven months later, showing new retinal hemorrhages and cotton-wool exudates, and small plexus of dilated capillaries.

DIABETIC RETINITIS PROLIFERANS

Case 13.—M. B., a Negro woman aged 53, was found to have diabetes in 1943. At that time, she had many small hemorrhages and irregular waxy exudates in each retina. In May 1945, new-formed vessels and fibrous tissue began growing into the vitreous of the right eye from the upper temporal portion of the retina and from the disk. The retinitis proliferans progressed, and on April 1, 1946 (fig. 21) roentgen therapy (4,000 r) was begun to the right eye. The new-formed vessels collapsed completely within seven weeks, and the fibrosis became slightly less (fig. 22). New retinal hemorrhages have since occurred from time to time, but there has been no recurrence of retinitis proliferans during the five months since roentgen therapy.

Case 14.—I. W., a white man aged 42, had a history of diabetes of three years' duration and of blurred vision for nine months. Examination March 27,

1946 showed multiple retinal hemorrhages and hard, white exudates and considerable retinitis proliferans, including many new-formed vessels, in each eye. Roentgen therapy (4,000 r to each eye) resulted in marked diminution, but not complete

Fig. 21 (case 13; April 1, 1946).—Right eye immediately preceding roentgen therapy.

Fig. 22 (case 14; June 4, 1946).—Right eye after completion of therapy (4,000 r), showing disappearance of new-formed vessels.

collapse, of the new-formed vessels, with temporary improvement of vision. However, the patient returned five months later with fresh vitreous hemorrhages and greatly reduced vision in each eye.

SUMMARY OF MATERIAL

The ocular diseases in these 14 patients did not constitute a single entity, but all the 22 eyes treated had in common retinal and vitreous hemorrhages with progressive formation of new vessels and fibrous tissue on the surface of the disk or retina and extending more or less into the vitreous. In every case the new-formed vessels and fibrosis could be called "retinitis proliferans," provided this term be used in a purely descriptive sense.

The ocular disease was classified as "typical" Eales's disease in 8 patients. This group consisted of 6 men and 2 women, all young, with bilateral recurrent retinal and vitreous hemorrhages of obscure origin and with retinitis proliferans. One patient had evidence of old healed bilateral anterior uveitis; 3 others had had probable unilateral choroiditis at some time before they were examined, and in a fifth patient an eye enucleated without having had roentgen therapy showed a nonspecific inflammatory occlusion of the retinal vessels. Reactions to tuberculin were positive in 6 of these 8 patients, 5 of them giving a positive reaction to the small dose of 0.001 mg. of old tuberculin U. S. P. injected intracutaneously and the sixth having shown a positive reaction to an unstated quantity given elsewhere. One of the patients in this group was insensitive to 1 mg. of old tuberculin given intracutaneously, but a roentgenogram of the chest showed enlarged hilar nodes. The final patient did not react to a patch test with a 1 : 10,000 dilution of old tuberculin, and the test was not carried further. These patients represented various occupations—business man, lawyer, seaman, clerk, housewife and army officer.

The ocular disease was classified as "atypical" Eales's disease in 4 patients. In 1 of these patients the only affected eye showed probable partial occlusion of several retinal veins, which may have initiated the process. A second patient had hemorrhages recurring at first only in a localized area of the only involved eye and showed an anomalous, sharply localized narrowing of the retinal vein supplying this area. A third patient, with bilateral involvement, showed two localized dilatations of retinal veins and probable localized occlusion and recanalization of another small vein. The fourth patient had classic aphthous uveitis.

The ocular disease was classified as diabetic retinitis proliferans in 2 patients. Both patients had long-standing diabetes with bilateral diabetic retinopathy, including retinal hemorrhages and exudates but little evidence of hemorrhages in the vitreous except for a faint haze. Typical retinitis proliferans had developed in the 3 eyes which were treated.

SUMMARY OF RESULTS

The first, and most striking, effect of roentgen therapy was a diminution in the new-formed vessels. The smaller vessels began shrinking within two to three weeks after therapy was begun and invariably disappeared from ophthalmoscopic visibility within four to eight weeks, even if the total dose was only 3,500 r. If a dose of not more than 4,000 r was given, the larger new-formed vessels usually showed some shrinkage in caliber but remained patent indefinitely. However, in the 6 eyes which received a total dose of 10,000 r or more, even the largest new vessels completely disappeared from ophthalmoscopic visibility. There has as yet been no definite recurrence of new-formed vessels in any of the 22 eyes treated.

Regression of fibrosis was less striking than the regression of vessels. If the fibrosis was scanty, almost translucent, before therapy began and if 10,000 r or more was given, the regression of fibrous tissue was marked. However, dense fibrosis, of long duration, was reduced only slightly or moderately even with heavy dosage, and doses of only 4,000 r had little effect, even on scanty fibrosis.

The tiny dilatations of retinal venules in 2 cases appeared to be less prominent but were still present after large doses of roentgen radiation, and the varicosities of the tiny retinal venules showed no perceptible change.

In the group of 8 patients with "typical" Eales's disease there has been only one recurrent hemorrhage. It consisted of two small retinal hemorrhages and a faint vitreous haze in an eye which had received only 4,000 r and did not show complete collapse of the larger new-formed vessels. This cessation of recurrent hemorrhages appeared to be more than a coincidence in 3 of these patients, in whom many small vitreous hemorrhages had appeared in each eye at intervals of one to four weeks, right up to the beginning of therapy. However, this cessation of hemorrhages may well have been the result of the breaking up of a "vicious cycle" (see "Comment"), rather than an effect on factors initially responsible for the ocular diseases. It must be emphasized that these results are only immediate, short term results, since only 4 patients have been followed longer than ten months. As we do not know the primary cause of the retinal and vitreous hemorrhages, we cannot report at present on the effects of the treatment in this regard, nor can we yet determine the permanency of the immediate effects.

In the group of 4 patients with "atypical" Eales's disease, there has as yet been a recurrent hemorrhage only in the patient with an anomalous localized constriction of a retinal vein. However, there has not yet been an appreciable follow-up period for the other 3 patients.

In the 2 patients with diabetic retinitis proliferans, fresh retinal hemorrhages have continued to appear, and in 1 patient fresh vitreous hemorrhages developed five months after therapy, even though the new-formed vessels were markedly diminished. It seems unlikely that roentgen therapy could result in permanent benefit for patients in this category until an effective treatment for diabetic retinopathy itself has been discovered.

COMMENT

Most retinal and vitreous hemorrhages gradually absorb without inducing retinitis proliferans, but sometimes, especially with recurrent hemorrhages, there is proliferation of new vessels and of fibrous tissue on the surface of the retina or disk and into the vitreous. Regardless of the primary cause of the hemorrhages, it is probable that this stimulation of new tissue formation is often a direct result of some factor of blood in the vitreous, although the components of blood which may be responsible for such a proliferative reaction are not known.

Small peripheral vitreous hemorrhages may result in retinitis proliferans arising from the disk, even though no blood pigment is visible in the vitreous around the disk. Further, retinitis proliferans may result from diabetic retinopathy, and progression into the vitreous may continue even when no actual blood cells are visible in the vitreous. These observations suggest the possibility that some factor in blood serum alone may stimulate such proliferation, although the presence of hemolyzed cells not visible ophthalmoscopically cannot be ruled out in such conditions.

The new-formed vessels extending into the vitreous have very thin walls and histologically are surrounded by a zone of homogeneous transudate and delicate sheets of fibroblasts. The thin walls of these vessels can certainly break, with actual seepage of blood into the vitreous, as we have observed in 2 cases. Also, it is theoretically possible that a transudate of serum from the thin-walled, new-formed vessels themselves may account for continued proliferation of new vessels even after the primary retinal and vitreous hemorrhages have cleared. Thus, in certain instances a vicious cycle may be established, the new, thin-walled vessels in the vitreous stimulating their own progression by actual hemorrhage, or possibly by simple transudation of serum. Our use of roentgen therapy has been directed primarily toward the destruction of new-formed vessels in the vitreous. If the vicious cycle just described plays as large a role in progressive retinitis proliferans as we believe, the results of roentgen therapy may prove to be permanent in those cases in which the primary cause of the hemorrhages is self limited, rather than of indefinite duration. This happy result cannot be hoped for in cases of diabetes but may be in many cases of Eales's disease.

The varicosities and tiny dilatations in retinal venules described in 3 of these cases all occurred in areas where retinal hemorrhages had been absorbed. For many years these vascular changes have been known to result at times from retinal hemorrhage and to remain permanently after absorption of the hemorrhage. It seems unlikely that they induce more hemorrhages or retinitis proliferans. The vessels are not newly formed, and they show little, if any, shrinkage as a result of even massive roentgen therapy.

We have purposely avoided the clinical terms periphlebitis and periarteritis because, while these terms denote actual inflammation around vessels, they are commonly used to indicate perivascular streaking. As a matter of fact, perivascular streaking is not necessarily indicative of an inflammatory process, but represents merely a sequela of absorption of large retinal hemorrhages in the areas supplied by the vessels.

A discussion of the etiologic factors in Eales's disease is outside the scope of this paper. Eales's disease may (reportedly) be caused by tuberculosis, glandular disturbance (such as menstruation), thromboangiitis obliterans, hemophilia, capillary fragility, thrombopenic purpura, ocular hypotony, low blood calcium, high blood pressure, low blood pressure and foci of infection. We suggest a primary vascular neoplasia, such as atypical angiomatosis retinae, as another cause—certainly, the end results are pathologically similar. In any event, we are unable even to give a concise definition of Eales's disease, let alone evaluate the primary causes and explain the facts that 80 per cent of the cases are of males and that the disease is usually bilateral.

SUMMARY

Intensive roentgen therapy to the posterior ocular segment was given during the eighteen months prior to this report in a series of patients with ocular diseases characterized by retinal and vitreous hemorrhages and by new-formed blood vessels and fibrous tissue extending from the retina or disk into the vitreous (retinitis proliferans).

A total of 22 eyes in 14 patients were treated. The ocular diseases were classified as typical Eales's disease, in 8 patients; atypical Eales's disease, in 4 patients, and diabetic retinitis proliferans, in 2 patients.

The irradiation technic devised by Martin and Reese for the treatment of retinoblastoma was utilized to avoid damage to the anterior ocular segment. A total dose of 3,500 to 15,000 r was given each eye treated. Doses of approximately 6,000 r are probably optimal.

Depending on the dose of roentgen radiation given, there were moderate to complete collapse of new-formed vessels and variable regression of fibrosis. There has been only one recurrent hemorrhage following treatment in the 8 cases of typical Eales's disease, an effect which has appeared to be of immediate significance, but the perma-

nency of these immediate results is not established because sufficient time has not elapsed since the patients were treated. In the 2 patients with diabetic retinitis proliferans, hemorrhages have continued to appear since treatment, and permanent beneficial results can hardly be expected.

Wilmer Ophthalmological Institute, Baltimore (Dr. Guyton).
Institute of Ophthalmology of Presbyterian Hospital (Dr. Reese).

DISCUSSION

Dr. Moacyr E. Alvaro, São Paulo, Brazil: The roentgen treatment of hemorrhagic alterations of the retina dates back to the end of the second decade of this century; curiously, it was through analogy with the good results obtained in the treatment of hemorrhages in cases of myoma uteri that Hessberg, in 1919, tried the roentgen treatment for hemorrhagic glaucoma. In the following years roentgen irradiation for hemorrhagic conditions of the fundus has met with increasing favor. However, there appears still to be considerable difference of opinion regarding the results. A subtantial group, comprising the great majority of those who have reported cases of retinal hemorrhages treated with roentgen radiation, seems to approve of the method and advocates the use of small doses, totaling 600 r, or even less. Thus, Basile, Saul, Zingale, Loewenstein, Reise, Schmerer, Hessberg, di Marzio, Jendralski and others have reported good results. Another group, however, is less enthusiastic. Cordes favored roentgen therapy only for tuberculous periphlebitis in young persons and discouraged it for vascular occlusion due to sclerosis. Schnyder and Foster cautioned against producing inflammatory conditions, which, in turn, might cause retinal detachment. Von Grósz warned of the possibility of hemorrhages due to roentgen radiation, and Stock, Mylius and Lorey reported cases in which this actually happened; in these cases, however, larger doses had invariably been given.

According to the general consensus, the action of the roentgen rays is always bionegative. The so-called stimulating action is apparently indirect, through catabolic substances produced by the primary destructive action of the rays on the tissues, through changes in the globulin-albumin ratio and through changes in the p_H.

An electron can be depicted as a small bullet 1 mm. in diameter revolving in a sphere—the atom—about 50 to 100 meters in diameter; the protein molecule has from 800 to 1,500 atoms, and a cell from 1,000,000 to 100,000,000,000 molecules. The impact of one of those electrons on the minute part of a cell which stops it (absorbs the rays) may cause several reactions. According to Dessauer, it produces heat, which coagulates some of the albumin of the cell. According to others, it produces changes in the electric charge of the colloids. Be it one or the other, or still some other phenomenon, the fact remains that there will always be changes as the result of the impact—changes in the ion concentration of mineral salts, in the cholesterol contents, in the viscosity of the plasma and in the permeability of cellular membranes.

Sensitivity to roentgen rays varies considerably from cell to cell in the different biologic species, and even in the same species, according to the type of cell. The more differentiated the cell, the less sensitive

it is. The action is always directly proportional to the activity of the cell, newly formed tissue being always more receptive.

White blood cells, having nuclei, are more sensitive to roentgen radiation than are red blood cells, except in vitro. Lymphocytes are the most sensitive of all, the sensitivity decreasing in the following order: monocytes, eosinophils, myelocytes and neutrophils.

The effect of roentgen rays on the blood vessels varies with the amount of radiation used. In the retinal blood vessels histologically studied by Hoffmann in enucleated eyes which had been given large doses of roentgen radiation in treatment of malignant tumors, there appeared to be considerable dilatation of both arteries and veins, with changes in the endothelial cells, where the nuclei showed pronounced tumefaction; moreover, there could be seen fibroblasts in great numbers, as in intense proliferation of the intima, and even consequent closing of the lumen of the vessels. When smaller doses are used, there is immediate dilatation of the capillaries, as proved by David and Gabriel in their experiments. In order to explain the vasodilatation, several theories have been proposed. 1. According to Best, Date and Dudley, roentgen rays are able to liberate histidine and similar substances from the tissues. Histidine is then tranformed into histamine, which, in turn, once in the circulating blood, causes the capillaries to dilate. 2. According to Ellinger, roentgen radiation acts directly on the nuclei of the endothelial cells, which appear to be very sensitive to these rays. This action would explain the changes observed in the intima, even in larger blood vessels. 3. According to the investigations of Sunder Plassmann, nerve terminations, in contrast to other nerve tissue, are very sensitive to roentgen rays. In his experiments he was able to show that the nerve terminations, which normally form a reticulum, after small doses of roentgen radiation had the appearance of a conglomerate mass. Thus, the roentgen rays would influence directly the terminal vasomotor branches, as has been shown by Jungenburg and Schlepakow in roentgen treatment of the thyroid gland. There is no reason that the roentgen rays could not have the same effect on the terminations of the vasomotor nerves in the vessels of the retina. Even with small doses, there seems always to be an increase in permeability of the endothelium of the capillaries, enabling a more active exchange of fluids between the circulating blood and the adjacent tissues.

What happens in the retina when hemorrhages occur? The blood flowing out of the blood vessels will be found to spread superficially among the nerve fibers, the hemorrhage then having the form of a candle flame; or it will penetrate more deeply between the fibers and take on a globular form, or it will break through the internal limiting membrane and into the vitreous. These hemorrhages can be rapidly resorbed without leaving any residue; but, more often than not, especially if they recur, degenerative changes may appear, and deposits of substances arising from disintegration of nerve cells, such as cholesterol and other lipids, may be found, as in glial or conjunctival proliferation. The time in which a hemorrhage will be completely resorbed varies from four days to weeks, months, or even years. In general, the larger the hemorrhage, the longer it will take to disappear; and the longer the disintegrating blood cells stay in direct contact with the adjacent nerve cells of the retina, the more harmful it is for the latter.

When the retinal hemorrhage is due to a stoppage in the blood flow, whether it be in an artery or in a vein, a certain portion of the retina, dependent for its nourishment on the impaired vessel, will deteriorate. In the case of arterial stoppage, the circulation of the blood may be reinstated through an existing anastomosis, as in the coexistence of the two systems—central artery and cilioretinal artery—or through new-formed blood vessels, and in both cases through gradual enlargement of the caliber of the aforementioned vessels. When the stoppage is in venous vessels, the reinstatement of circulation of the blood will be even more rapid, through adjacent veins, through enlarged capillaries or through anastomosis with choroidal vessels. Moreover, the blood clot can be perforated by one or several channels, and circulation along the occluded vein itself can be resumed. At the same time, small collateral blood vessels are gradually enlarged. At first, they cannot be seen ophthalmoscopically; if they are over the optic disk, they may give the impression of hyperemia, or, if over the retina, they may look like small hemorrhages. Gradually, however, they become visible with the ophthalmoscope and can easily be recognized by their typical appearance of a mesh or of tortuous vessels with many anastomoses, forming a true rete mirabile. These new-formed vessels apparently have no purpose, but actually they reestablish the impaired circulation of the blood. The longer any portion of the retina remains deprived of nourishment through lack of circulating blood, the more it deteriorates; and the chances are that the blood vessels adjacent to that part will, in turn, acquire changes which later will cause new hemorrhages. Thus, the sooner the circulation of blood is restored, the better will be the prognosis.

In cases of retinitis proliferans one should discriminate between those in which, after retinal hemorrhages, fibrous tracts from the conjunctiva with few blood vessels are formed at the optical disk and make their way into the vitreous, and other cases in which only a very thin layer of semitransparent conjunctival fibrous tissue sustains a rete mirabile of blood vessels. In the first type the condition is a true retinitis proliferans, whereas in the second type the new-formed blood vessels are the expression of an effort to reestablish normal blood flow in a section of the retina where blood circulation was abolished or impaired through the closing of the lumen of arteries or veins.

Retinitis proliferans in cases of the second type, retinal hemorrhages due to various causes, as in the complex generally known as Eales's disease, and retinal changes due to arteritis and both periphlebitis and endophlebitis can all be successfully treated with small doses of roentgen radiation. Vascular dilatation and increased permeability of the endothelium of the capillaries will be accessory to improvement in circulation of the blood, so that insufficient nutrition of the adjacent retina, and ultimately fresh hemorrhages, are avoided and the process of resorption of the existing blood among the nerve cells is hastened. In these cases it would be advisable to use very small doses, of 50 r, at intervals of five days. Miescher's three wave theory indicates that this should be the ideal interval, as the second treatment would coincide with the interval between the first and the second wave, when capillary dilatation would have reached its lowest point.

True retinitis proliferans, of the first type, in which there are fewer new-formed blood vessels and more fibrous tissue tracts, does not respond to small doses of roentgen radiation. It is advisable to use larger doses,

when tumefaction of the nuclei of the endothelium and accumulation of fibroblasts, as in proliferation of the muscular layer, may bring about occlusion of the lumen, with discontinuation of the blood flow, thus breaking up the "vicious circle," which, as the authors have pointed out, may be responsible for fresh hemorrhages. An action on the plasma, increasing its viscosity, might also be considered. The higher sensitivity of the new-formed blood vessels to the roentgen rays explains the excellent results which were obtained.

When small doses of roentgen radiation are given, the anterior portal may be used, as then no damage can be done to the cornea or to the lens, sensitivity of these structures to roentgen rays being much lower than that of the retinal blood vessels. The cornea begins to react only when 800 r is reached, and the crystalline lens only when 500 r is given, whereas 50 r suffices for dilatation of the retinal capillaries. For larger doses, such as those which were used by Dr. Guyton and Dr. Reese, the temporal portal, or the nasal portal when there is no hindrance, should be used.

For roentgen therapy of the retina in its posterior pole, high voltage rays are advisable, as 100 per cent, or even 105 per cent, of the radiation reaches the retina, as a result of the addition of secondary rays, whereas low voltage rays lose their power and only 25 per cent reaches the posterior pole of the globe.

Roentgen treatment for repeated retinal hemorrhages of various kinds and for retinitis proliferans is justified both by the clinical results seen in the last ten years and by knowledge of its modus operandi. Moreover, the difficulty in establishing the true etiologic diagnosis in many cases and, as a consequence, the unlikelihood of combating the disease by destroying its primary cause must, perforce, encourage the pathogenic approach to therapy.

The excellent results reported by Dr. Guyton and Dr. Reese with roentgen therapy on 22 eyes with posthemorrhagic new-formed blood vessels in the retina justify my suggestion of the general use of this method, so that a larger number of cases, to be observed over a long period, may enable us to reach definite conclusions.

DR. WILLIAM L. BENEDICT, Rochester, Minn.: Since the application of roentgen therapy to recurrent hemorrhages is not a new procedure, we must consider the variations of the older procedures that have been advocated and used by their authors.

We are somewhat familiar with the remote effects of radiation on ocular structures, even when the eye is not the objective of direct roentgen therapy; therefore, the use of roentgen therapy directed to fundal lesions has been restricted largely because of reticence in initiating pathologic changes that may progress in future years into fibrosis and general degeneration of ocular structures.

I have had no experience with concentrated, directed roentgen therapy, such as has been employed by the authors. I am familiar, however, with the application of roentgen rays in the absorption of extravasated blood in the vitreous and their immediate, and somewhat remote, effect on the proliferation of new retinal vessels.

I have noted the results of this method of treatment of hemorrhagic diseases of the eye in diabetic patients. I have been able to follow the effects over a period of from four to six years of mild doses of roentgen radiation applied directly to the eye, either temporally or through the

pupil. There is no question that blood in the vitreous will be absorbed much more rapidly after irradiation with a dose of 300 to 1,300 r than if the disease is not treated. I am well aware, however, that the retinopathy of diabetes progresses with the age of the patient rather than with the severity of the diabetes, and that the most extensive changes occur in persons whose diabetes begins early in life; regardless of the fact that the diabetes may be well controlled by diet or with the use of insulin, vascular changes progress, first on the venous side and later on the arterial side, and eventually proliferation of new vessels and fibrosis of old thrombosed vessels and hemorrhagic areas occur.

Later studies of the eyes so treated of persons who have had repeated hemorrhages into the vitreous and more or less extensive diabetic retinopathy have shown that the repeated hemorrhages into the vitreous, even of some duration, will disappear more rapidly after the application of comparatively small or mild doses of roentgen rays. However, the proliferative changes in the vessels are not noticeably affected. In no case have I observed diminution in the proliferation of new vessels.

Roentgen irradiation also has been advocated in the treatment of thrombosis or occlusion of the retinal vessels of one cause or another. In most of the patients whom I have treated, unfortunately, such extensive glaucomatous changes have developed that enucleation became necessary, and some other patients have not been followed.

In no case have I seen any definite improvement in the treatment of eyes in which an occlusion of the central vessels with hemorrhage has occurred. I treated a patient with thromboangiitis obliterans more than three years ago. There was no noticeable effect, but the doses used were small and only two applications were given, the total dose being not more than 725 r. I think, therefore, that the new development in this method of treatment consists in the direct application of the rays of high intensity or the use of large doses over very small areas. It is yet to be seen what effect such irradiation will have on the proliferation of vessels in far advanced stages and on the more extensive proliferations that occur not only in diabetic retinitis but sometimes in Eales's disease. There is no question that the immediate effect on the hemorrhagic extravasation to the vitreous will disappear. That, however, is a virtue that cannot be attributed to the high dosage alone.

I should like to know the authors' opinion regarding the value of direct, high-powered irradiation on the proliferation of vessels in cases of advanced diabetic retinopathy with proliferation, the so-called desperate cases, as well as what might be expected ultimately in fibrosis and degeneration of the retinal vessels.

DR. ALGERNON REESE, New York: We have not discussed etiology, first, because it is not within the scope of this paper and, second, because we do not know anything about it. As a matter of fact, we do not know even to what condition the term Eales's disease should be rightly applied. We do know that the term is used to designate a rather heterogeneous group of conditions, as already noted by Dr. Guyton.

Our impression is that Eales's disease proper is a bilateral infectious process having a prediliction for both the arteries and the veins of the retina, and frequently affecting also the uvea. The predilection of a causative agent for a certain type of tissue is not unusual. An example is the preference the herpes virus has for nerve tissue.

The purpose of our treatment is not to promote absorption of hemorrhage but to dissipate new-formed blood vessels from which hemorrhage might come. The cases in which the greatest benefit has followed the treatment have been those in which there was the greatest number of new-formed blood vessels of the "rete mirable" type, with a minimum amount of stroma and organized scar tissue. To date, this regression of the process has been followed by a decrease in the occurrence of retinal and vitreous hemorrhages. As Dr. Guyton emphasized, it is premature to say whether or not the regression and cessation of hemorrhages from this treatment will be permanent.

We are grateful to Dr. Alvaro for pointing out the rationale of the roentgen treatment in these cases. We agree with him that smaller doses of roentgen radiation suffice, and our tendency at present is to reduce the total dose.

Dr. Benedict has rightly emphasized that this treatment consists in directing the rays to the site of the lesion, to the exclusion of the vulnerable anterior part of the eye. This is the most important feature of the treatment and cannot be stressed too much. It is the reason we can give large doses with a minimum of untoward effects.

Dr. Benedict asked about the value of this treatment for diabetic retinopathy. Our experience in this regard is confined to 2 cases, in neither of which was the treatment of benefit. We hope to use the method in a sufficient number of cases to be able to assess the treatment in cases of diabetic retinopathy, in particular those with a large element of new-formed blood vessels.

STUDIES IN EXPERIMENTAL OCULAR TUBERCULOSIS

XII. Effect of Streptomycin and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit

ALAN C. WOODS, M.D.
AND
RONALD M. WOOD, B.S.
BALTIMORE

IN PREVIOUS communications [1] there were reported the results of experiments which dealt with the possible therapeutic effect of one antibiotic and two chemotherapeutic agents on experimental ocular tuberculosis. It was found [1a] that penicillin G, given in enormous doses, has no deterrent action on the progress of ocular tuberculosis in the normal (nonimmune) rabbit. It was further reported [1b,c] that two sulfones, "promin" (N,N′-didextrose sulfonate, the sodium salt of p,p′-diaminodiphenyl sulfone) and "promizole" (4,2′-diaminophenyl-5′-thiazolylsulfone) had a deterrent effect on the ocular disease. This was apparent in both the immune-allergic and the normal rabbit, although in the normal animal the effect was not marked. In the normal rabbit, a slight decrease in the ocular inflammation was noted at the end of the second week of treatment, and this was clinically most noticeable after eight weeks of treatment. However, transmission experiments of inoculum from the eyes of the treated animals at the termination of treatment all produced the disease. In the immune-allergic rabbits the effect of treatment was more pronounced. There was a noticeable difference in the clinical picture of the treated and that of the control group at the end of the third week of treatment, and at the conclusion of treat-

From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University.

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1. (*a*) Kennedy, J. O.; Woods, A. C.; Buckley, J.; Berthrong, M., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: IX. Failure of Penicillin to Affect the Course of Ocular Tuberculosis, Arch. Ophth. **39**:261 (March) 1948; (*b*) Woods, A. C., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: X. Effect of "Promin" and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, ibid. **39**:471 (April) 1948; (*c*) XI. Effect of "Promin" and "Promizole" on Experimental Ocular Tuberculosis in the Normal Rabbit, ibid. **40**:1 (July) 1948.

ment the histologic evidences of tuberculosis in the eyes of the treated animals were minimal as compared with those in the controls. Moreover, in transmission experiments, the eye of only 1 treated rabbit was found to be infectious. It was concluded that both "promin" and "promizole" had a limited bactericidal effect on Mycobacterium tuberculosis and that this therapeutic action became much more evident when a systemic immunity restrained the tuberculous process to limits within the therapeutic range of the drugs.

The observation immediately suggested that "promizole," a nontoxic sulfone which can be administered to human subjects in doses up to 12 or 15 Gm. per day without untoward symptoms, might happily be combined with such an antibiotic as streptomycin in the treatment of ocular tuberculosis. The classic investigations of Feldman and his associates have already conclusively demonstrated the strong deterrent and therapeutic action of streptomycin in experimental tuberculosis in the guinea pig. A recent report by Grignolo [2] on the action of streptomycin alone and of a combination of streptomycin and "promin" on experimental ocular tuberculosis in the normal rabbit indicates that such treatment, begun immediately after inoculation of the eyes, had an inhibitory effect on the later development of lesions during the course of treatment. However, tuberculous disease developed at varying intervals after the cessation of treatment. When treatment was instituted after lesions had appeared in the eyes, no deterrent or therapeutic action was observed.

There are numerous reports of favorable clinical action in various forms of human tuberculosis, but only fragmentary mention of its effect in clinical ocular tuberculosis. The early scarcity of streptomycin, the untoward side effect sometimes observed—vestibular damage, the development of sensitivity and the development of resistance to the drug by the Myco. tuberculosis, with the possibility that systemic lesions will be lighted up—all appear to have restrained ophthalmologists from using it in the treatment of clinical ocular tuberculosis. As a result, the occasional scattered mention of the use of streptomycin in cases of clinical ocular tuberculosis does not provide sufficient data to permit any conclusions as to the merits and danger of such therapy. It is evident that this field should be explored. It is also evident that, in view of the danger of recurrence after the maximum of streptomycin therapy has been given, happier therapeutic results might be obtained if some effective chemotherapeutic agent could be administered in conjunction with streptomycin and continued after streptomycin therapy has been terminated. A case in point was recently observed in the Wilmer

2. Grignolo, A.: Primi risultati spermentali e clinici sull'impiego della streptomicina nelle infezioni tubercolari dell'occhio, Minerva med. **1**:16, 1948.

Institute, that of a young Negro girl who had been energetically treated with streptomycin alone for tuberculous meningitis, from which she had made a complete symptomatic recovery. Three months after injections of streptomycin has been stopped, widespread, acute, caseating ocular tuberculosis developed in one eye, resulting in its loss.

The idea of combining an effective sulfone with streptomycin is not new. As early as 1945, Smith and McClosky [3] reported on the combination of streptomycin and "promin" in the treatment of experimental tuberculosis in mice and rats. They found the chemotherapeutic index of streptomycin ten times that of "promin," but the combination of streptomycin and "promin" gave three times the effect that might be expected from mere summation, indicating a synergistic action. In a later report,[4] in which their data were obtained from direct tissue smears, subculture of lung suspensions and subinoculation of lung suspensions in guinea pigs, they found little, or no, deterrent effect with "promin" alone and a moderate depressant action with streptomycin, but sterilization in 41.6 per cent of their animals after treatment with the two drugs. A recent clinical report by Lincoln and her associates [5] indicates favorable results in the treatment of miliary tuberculosis in children with "promizole" alone.

EXPERIMENTAL STUDY [6]

Determination of Dosage.—The first question to be determined was that of dosage. This had already been worked out for "promizole" by Feldman, and in the previous studies of this series it was found that 1 per cent "promizole" added to the diet provided an approximate daily dose of 1.25 Gm. of the substance and produced a blood level that ranged as high as 1.9 mg. per hundred cubic centimeters. This was the dose of "promizole" administered in this experiment.

In Feldman's original experimental work with streptomycin, the drug was given at six hour intervals. The usual practice is to administer streptomycin every three or six hours to clinical patients. Molitor,[7] for example, stressed the need of giving streptomycin every three hours in order to maintain an effective concentration. Recent investigations have clearly indicated, however, that such frequent administration is unnecessary to obtain the full therapeutic effect. Thus Feld-

3. Smith, M. I., and McClosky, W. T.: The Chemotherapeutic Effect of Streptomycin and Promin in Experimental Tuberculosis, Pub. Health Rep. **60**: 1129, 1945.

4. Smith, M. I.; McClosky, W. T., and Emmart, E. W.: Influence of Streptomycin and Promin in Proliferation of Tubercle Bacilli in the Tissue of the Albino Rat, Proc. Soc. Exper. Biol. & Med. **62**:157, 1946.

5. Lincoln, E. M.; Stone, S., and Hoffman, O. R.: The Treatment of Miliary Tuberculosis with Promizole, Bull. Johns Hopkins Hosp. **82**:56, 1948.

6. The streptomycin sulfate used in this experiment was given by Chas. Pfizer & Company, Inc., and the "promizole," by Parke, Davis & Company.

7. Molitor, H.: Pharmacology of Streptomycin, Bull. New York Acad. Med. **23**:196, 1947.

man [8] found in guinea pigs treated once, twice and four times daily, or four times daily on alternate weeks (all animals receiving the same amounts of streptomycin), that the numerical index of infection after a minimum of three weeks' treatment varied from 3.2 to 6.0 with the different doses, as compared with an index of 85.3 for the untreated controls. In other words, there was no practical difference in the therapeutic results when streptomycin was administered less often. Corper and Cohn [9] showed that the same effect in prolonging the lives of animals with an otherwise lethal infection was obtained when streptomycin was given every five days. The report by the Veterans Administration to the Council on Pharmacy and Chemistry of the American Medical Association [10] indicated that involvement of the vestibular branch of the eighth nerve occurred in 96 per cent of patients receiving 2.0 Gm. of streptomycin daily in divided doses. At the fourth Streptomycin Conference of the same groups, it was reported [11] that, in man, equally favorable therapeutic effects were obtained with, and the patients did quite as well on, 0.5 Gm. of streptomycin every twelve hours as they did on the same dose given more frequently, i. e., 0.5 Gm. every six hours. Further, the toxic reactions were much less, involvement of the vestibular branch of the eighth nerve occurring in only 17 per cent of the patients receiving 0.5 Gm. every twelve hours. The occurrence of other toxic reactions was less reduced, and no difference was found in the development of resistance by the isolated tubercle bacilli.

In the light of these investigations, the streptomycin in these experimental animals was administered once a day only. The dose was 50 mg. per kilogram of body weight. This dose was well tolerated. During the course of the experiment only 1 of the treated animals died, and this of an incidental cage infection, unrelated to tuberculosis or treatment. This mortality rate was well below that expected in the light of our previous experiments with tuberculous rabbits. This dose of "promizole" and streptomycin produced blood levels up to 7.6 mg. per hundred cubic centimeters for streptomycin, the blood being taken one and one-half hours after the administration of the streptomycin. The high level for "promizole" was 5.1 mg. per hundred cubic centimeters, and the mean of the various determinations was 1.7 mg. per hundred cubic centimeters.[12]

Plan of the Experiment.—On June 19, 1947, 66 rabbits were inoculated in the groin with 0.5 cc. of a six week old culture of a virulent human strain of Myco. tuberculosis. The rabbits were entirely asymptomatic, and on Jan. 22, 1948,

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8. Feldman, W. H.; Henshaw, C. H., and Karken, H. G.: Frequency of Administration of Streptomycin: Its Influence in Results of Treatment in Guinea Pigs, Am. Rev. Tuber. **55**:435, 1947.

9. Corper, H. J., and Cohn, M. L.: The Remote Sustained Threshold Therapeutic Action of Streptomycin in Tuberculosis, Science **106**:446, 1947.

10. The Effects of Streptomycin on Tuberculosis in Man, report of the Council on Pharmacy and Chemistry, J. A. M. A. **135**:634 (Nov. 8) 1947.

11. Dosage of Streptomycin in Tuberculosis, Current Comment, **135**:842 (Nov. 29) 1947.

12. The blood levels for both streptomycin and "promizole" were determined by Dr. E. Kennerly Marshall, Professor of Pharmacology of the Johns Hopkins University School of Medicine. The technic of determinations has been reported by Dr. Marshall and his associates (Marshall, E. K., Jr.; Blanchard, K. C., and Buhle, Emmett L.: Colorimetric Methods for Determination of Streptomycin, J. Pharmacol. & Exper. Therap. **90**:367, 1947).

there were 64 survivors, all in excellent condition. Intracutaneous tests with purified protein derivative U. S. P. showed that all rabbits had a moderate degree (1 plus reaction) of cutaneous hypersensitivity. On January 22, all the rabbits were given an injection into the anterior chamber of 0.2 cc. of the paper filtrate of a six week old culture of the same organisms so adjusted that each oil immersion field contained approximately 200 bacilli. At the time of the ocular inoculation, the sensitivity of this organism to streptomycin was determined, and it was found that the tubercle bacillus used was sensitive to 1 microgram per cubic centimeter of streptomycin.

All rabbits showed the usual immediate reaction to the tuberculin in the inoculum, manifested by ciliary congestion and the usual evidences of nongranulomatous iritis, the symptoms coming on twenty-four hours after the inoculation and lasting about three days. Thereafter, the eyes were practically asymptomatic for about ten days, when low grade ciliary congestion, slight haziness of the cornea and evidences of inflammation in the iris developed. By February 11, three weeks after inoculation, these symptoms were definite, and miliary tubercles appeared on the iris or in the cornea or in both. The degree of tuberculous activity in each rabbit was then evaluated on a numerical scale (0 to 4), just as was done in the former experiments in this series. The rabbits were then divided into three groups of 21 each, each group having tuberculous activity of the same average severity. In actual figures, group 1, the control group, had an average reaction of 0.8; group 2, which received streptomycin alone, an average reaction of 1.0, and group 3, which received both streptomycin and "promizole,'" an average reaction of 1.1. Thus, the figures were weighted slightly against the treated animals in that they represented severer initial reactions than did those for the control series. Treatment was started on February 11, with the dose already outlined, group 1 receiving no treatment; group 2 received 50 mg. of streptomycin alone in one daily injection; group 3 received the same amount of streptomycin per kilogram of body weight plus 1 per cent "promizole" added to their food. Thereafter, each animal was examined carefully clinically once a week; the degree and intensity of ocular tuberculosis were estimated, and the average activity for each group was thus determined and recorded.

On April 27, when treatment was terminated, 6 animals from group 1 (fair specimens of the control group, with an average activity of 1, this being the average for the entire group), 6 animals of group 2 and 6 animals of group 3 were killed and autopsied and their eyes removed for histologic section. Six other rabbits, of groups 1, 2 and 3, were similarly killed and the injected eyes removed. These eyes were opened under aseptic precautions, and the uveal tracts dissected out and ground up in a test tube with sterile sand in 1.5 cc. of sterile saline solution. The supernatant fluid was decanted and cultured; 0.2 cc. of this extract of the uveal tract was injected in the anterior chamber of the eye of a normal rabbit to determine whether the uveal tracts of the control and the treated animals were infectious. The remaining rabbits, 8 in group 1 (controls), 7 in group 2 and 8 in group 3, were kept for further observation to determine whether there were any recurrences after cessation of treatment.

RESULTS

Clinical Course.—The composite results of the clinical courses of the three groups are shown in figure 1, in which the ordinate represents the degree of the average intensity of the ocular tuberculosis and the

abscissa represents the time, in weeks. Thus, at the end of one week of treatment there was a slight, but statistically insignificant, change in favor of the two treated groups. At the end of the two weeks, this change was pronounced, and at the end of the fourth week it was most striking. At this time the disease in the control group had advanced and the average activity of the group was 2, while the average for the two treated groups had dropped to 0.26 and 0.25, respectively. While the figures for group 2 and group 3 were identical at this time, the general improvement was much more striking in group 3, treated with the combination of streptomycin and "promizole." Thus, in group 2, there were 6 animals with activity rated as 0 (completely inactive clinically) and 6 rated as showing a trace of activity, while 7 had activity. In group 3, 11 animals were rated as showing no activity, and 6, as showing only a trace, while only 3 had activity. One appar-

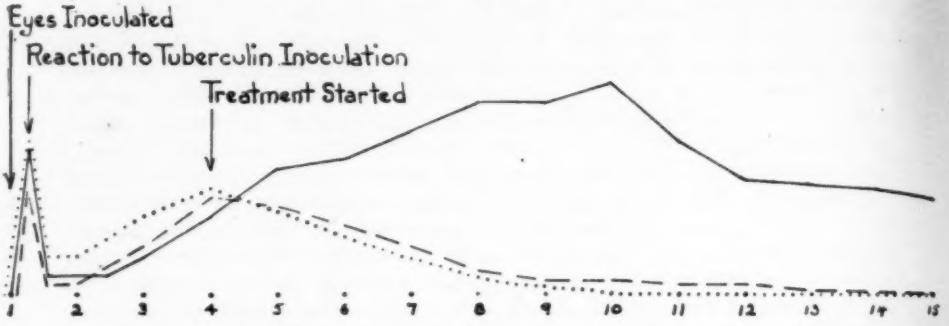


Fig. 1.—Graph illustrating clinical course in rabbits of groups 1, 2 and 3. The values for the untreated group (group 1) are shown by the solid line; those for the group treated with streptomycin alone (group 2), by the line of dashes, and those for the group treated with streptomycin and "promizole," by the line of dots.

The intervals indicated on the line of ordinates represent 0.1 on the numerical scale used for grading tuberculous activity.

ently nonimmune rabbit with severe and resistant ocular tuberculosis accounted for the greater part of the activity in group 3 at this time.

On March 23, after six weeks of treatment, the untreated (control) group was at its height of activity, the average being 2.2. At the same time, in group 2, there were 12 rabbits with a rating of 0 and 6 with only a trace of activity, while only 3 were rated as showing activity. In group 3, 14 rabbits were given a rating of 0 clinically, and the remaining 6 showed only a trace of activity, none being rated as having active tuberculosis. On April 6, after eight weeks of treatment, all rabbits in the control group had activity, although the tuberculous inflammation was definitely declining, the average rating being 1.3. In group 2, 15 rabbits had a rating of 0, and the remaining 4 showed only a trace of activity. In group 3, all 20 rabbits had a rating of 0, showing only

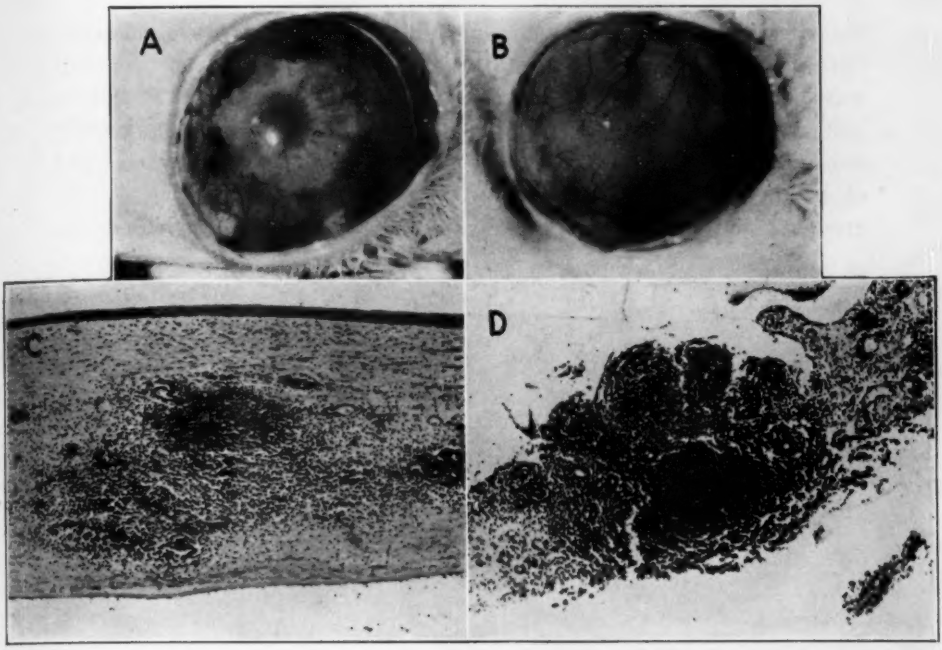


Fig. 2 (rabbit 7, group 1).—*A*, cornea on February 25; *B*, cornea on April 28; *C*, cornea showing scattered hard tubercles; *D*, iris with a large, hard tubercle.

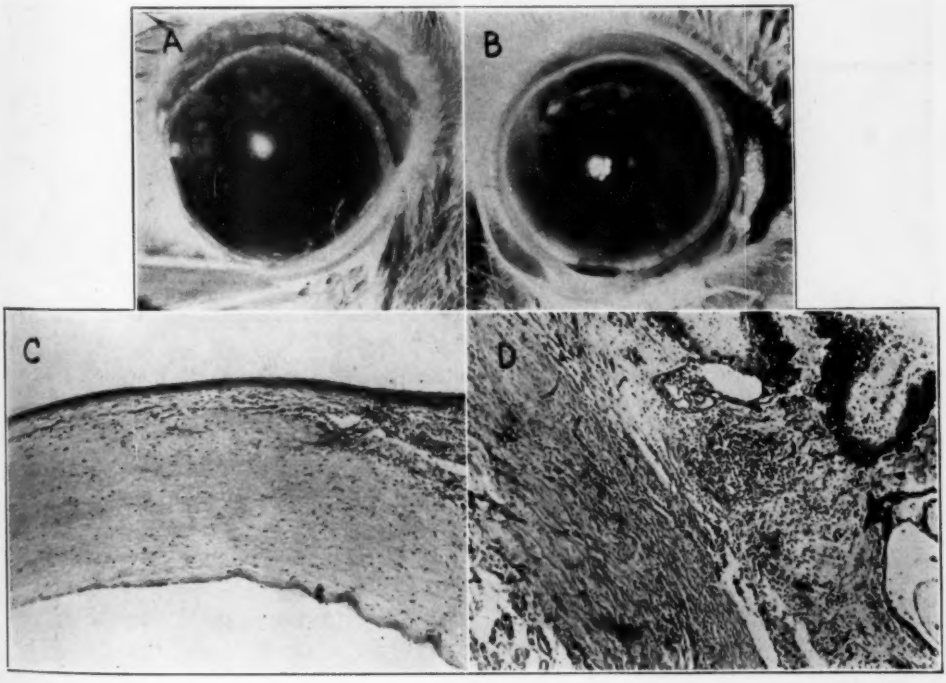


Fig. 3 (rabbit 14, group 1).—*A*, eye on February 25; *B*, eye on April 28; *C*, cornea, showing moderate infiltration; *D*, root of iris and ciliary body, showing small, hard tubercle and epithelial and monocellular cell infiltration.

the scars of the former inflammation and no traces of activity whatsoever. On April 27, seventeen weeks after the inoculation, the control group was beginning to show the usual spontaneous healing observed in immune-allergic rabbits, 3 animals being recorded as showing no activity and 2 others as showing only a trace, while the remaining 15 were recorded as having definite activity, the average for the group being 1. In groups 2 and 3, the activity of all rabbits was rated as 0, there being

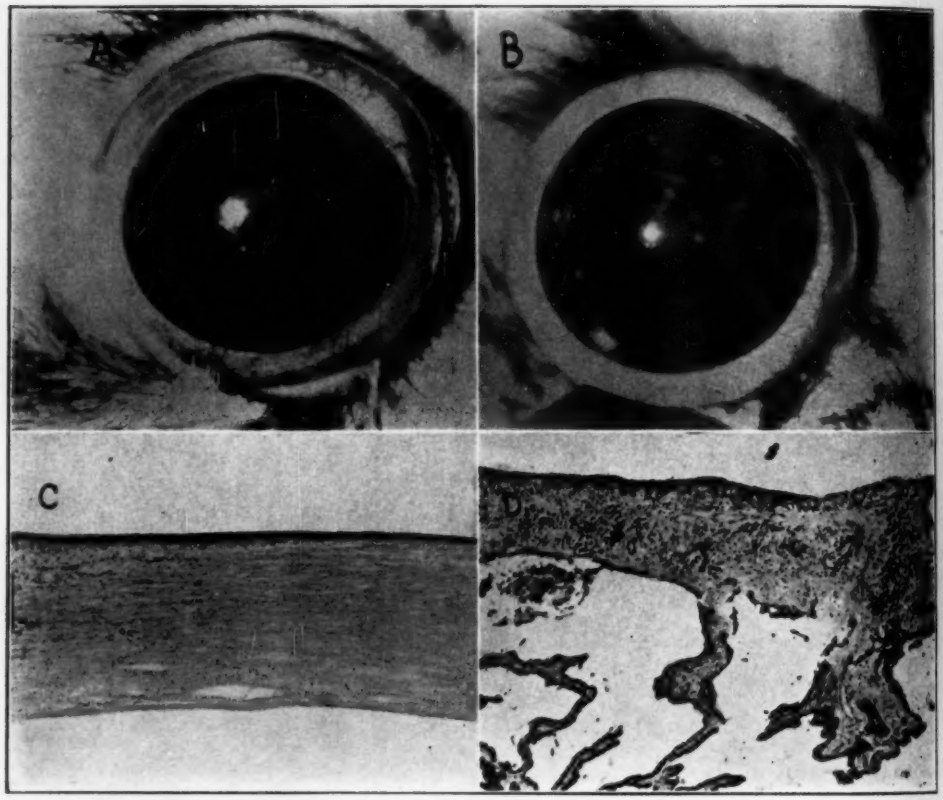


Fig. 4 (rabbit 13; group 2).—*A*, eye on February 25, at beginning of streptomycin therapy; *B*, eye on April 28, after completion of streptomycin therapy; *C*, cornea and limbus, showing minimal infiltration of cornea; *D*, iris, showing small active tubercle on posterior surface and healed tubercle of stroma.

no trace of any active inflammation in any of the treated animals. Treatment was stopped on this date. *A* and *B* of figure 2 are photographs of the eye of an untreated (control) rabbit (group 1, rabbit 7) taken on February 11 and April 27, respectively. This rabbit was the most severely affected of the untreated group. *A* and *B* of figure 3 show the eye of another untreated control, the least severely affected of the rabbits of

group 1, taken on the same dates. These photographs therefore illustrate the high and low extremes of untreated ocular tuberculosis in immune-allergic rabbits.

The clinical appearance of 2 rabbits of group 2, before and after treatment, are shown in figures 4 *A* and *B* (rabbit 13) and 5 *A* and *B* (rabbit 17), which illustrate the fading of ciliary congestion, the clearing of the cornea and the absorption of the tubercles in the iris.

The course of the disease in the rabbits of group 3 is shown in figures 6 *A* and *B* (rabbit 35) and 7 *A* and *B* (rabbit 37). These

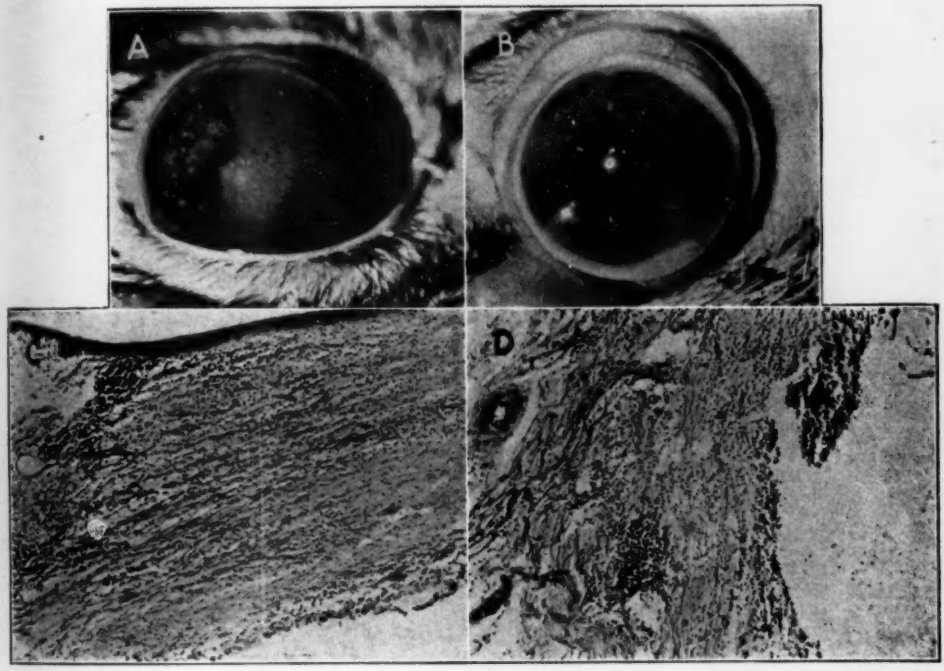


Fig. 5 (rabbit 17; group 2).—*A*, eye on February 25, at beginning of streptomycin therapy; *B*, eye on April 28, after completion of streptomycin therapy; *C*, minimal infiltration of limbus and root of iris; *D*, root of iris and ciliary body, showing small tubercle and moderately intense cellular infiltration.

figures illustrate the more dramatic clinical results shown by the animals treated with the combination of streptomycin and "promizole." Thus, figures 6 *A* and 7 *A* show the appearance of the eyes on February 11, when treatment was started, with ciliary congestion, moderate uveal inflammation, contracted pupil and many tubercles scattered over the surface of the iris, and figures 6 *B* and 7 *B* illustrate the appearance on April 27, with complete absorption of the tubercles of the cornea and iris.

Histologic Features.—Histologic examination of the eyes of the rabbits killed for study showed a distinct difference in the pictures of the three groups.

GROUP 1 (untreated controls): The picture was that usually seen in the secondarily inoculated eyes of immune-allergic rabbits. There were numerous hard tubercles throughout the cornea, iris and ciliary body, with moderate to severe mononuclear and epithelioid cell infiltration of the angle, iris and ciliary region. Only occasionally were any areas of caseation and necrosis noted. There were practically no lesions anywhere in the posterior ocular segment.

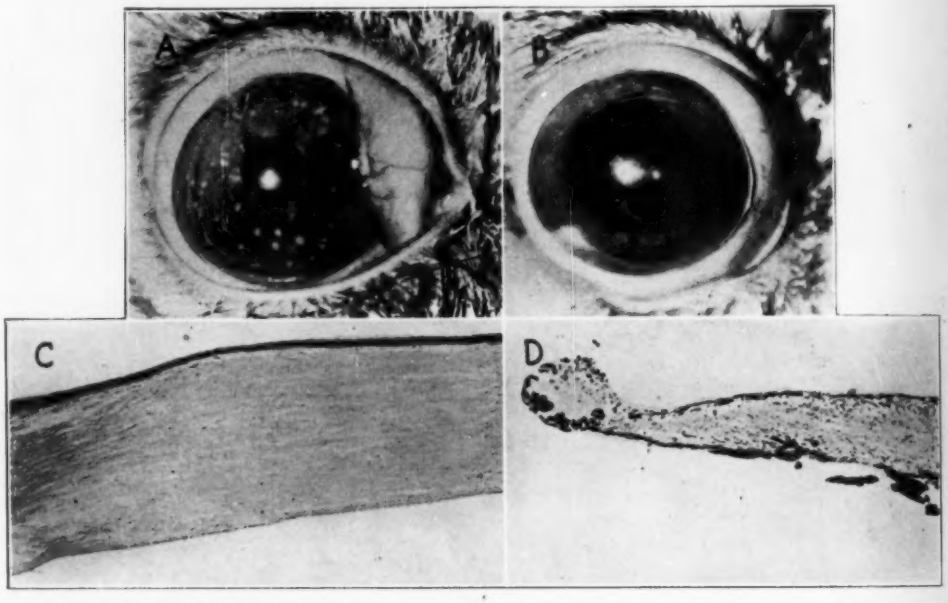


Fig. 6 (rabbit 35, group 3.—*A*, eye on February 25, before beginning of streptomycin and "promizole" therapy; *B*, eye on April 28, after completion of therapy; *C*, cornea, showing minimal scarring; *D*, healed tubercle on tip of iris.

The appearance of the eyes of the rabbits of group 1 is illustrated in figures 2 *C* and *D* and 3 *C* and *D*. In the most severely involved of the controls (rabbit 7; figs. 2 *C* and *D*) there were dense cellular infiltration, with many large, hard tubercles and one area of caseation and necrosis (not shown in figure). *C* and *D* of figure 3 show, respectively, the cornea near the limbus and the iris and ciliary body of the least severely involved of the animals of group 1 (rabbit 14). There was moderately severe infiltration of the cornea near the limbus; elsewhere the cornea was clear. The iris and ciliary body were more severely involved, showing hard tubercles and some diffuse cellular infiltration.

GROUP 2 (treatment with streptomycin alone): The picture was much less severe than that in the untreated controls. Careful study of the sections, however, revealed in all eyes minimal to moderate evidences of active tuberculosis. Such evidences consisted in occasional

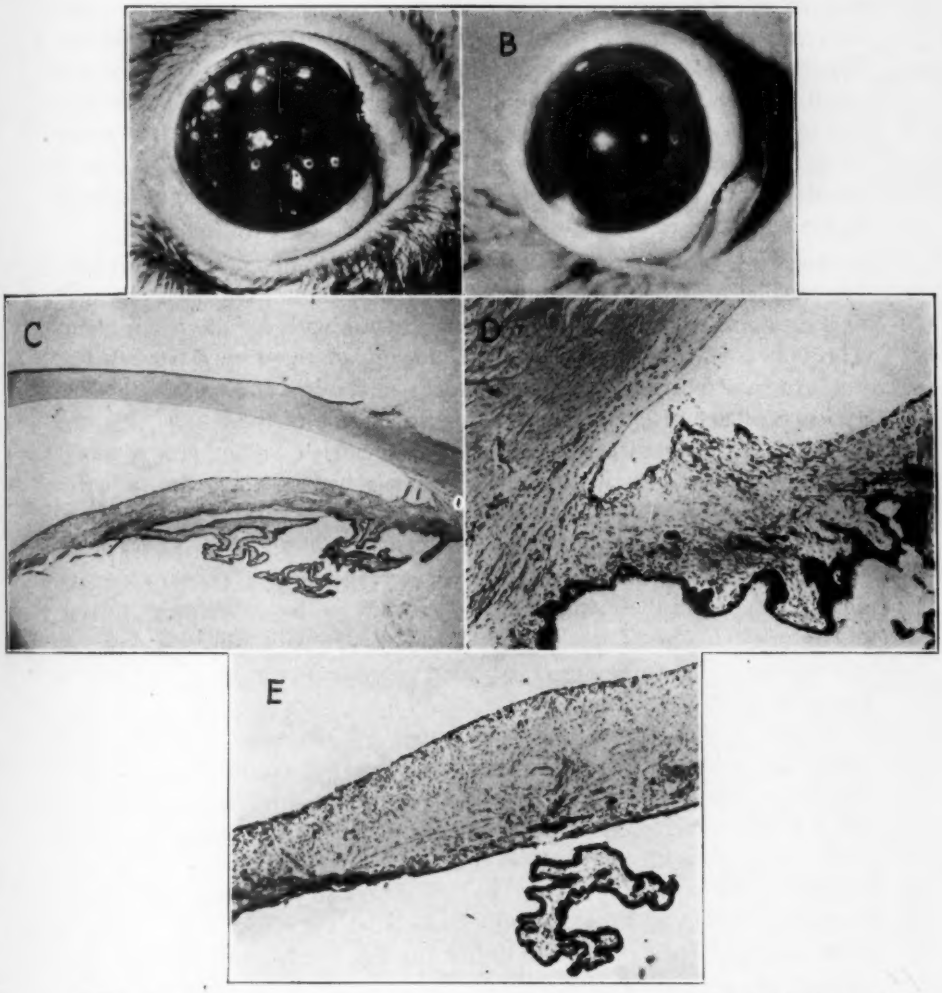


Fig. 7 (rabbit 37, group 3).—*A*, eye on February 25, before beginning of streptomycin and "promizole" therapy; *B*, eye on April 28, after completion of therapy; *C*, anterior segment, showing normal cornea; *D*, root of iris, showing possible minimal infiltration with scarring, and *E*, iris with few persisting wandering cells.

areas of mononuclear and epithelioid cell infiltration and in occasional small tubercles, usually on the posterior surface of the iris rather than in the stroma, giving the impression that the tubercle bacilli fared rather

better in the ocular fluids than in the stroma. There was abundant scarring, and in many places healed tubercles occurred. However, every eye examined in this group still showed histologic evidence of at least minimal activity.

Typical lesions of the rabbits of group 2 are shown in figures 4 *C* and *D* and 5 *C* and *D*. These sections show slight, but definite, evidences of smoldering activity, despite the negative clinical appearance. Figure 4 *C* shows minimal infiltration of the cornea; figure 4 *D*, a very small tubercle, or Koeppe nodule, on the posterior surface of the iris, free in the posterior chamber. Figure 5 *C* shows minimal infiltration in the cornea near the limbus in rabbit 17, while figure 5 *D* shows a small tubercle near the root of the iris and moderate cellular infiltration in the ciliary area.

GROUP 3 (treatment with a combination of streptomycin and "promizole"): Histologic evidences of tuberculosis was much less than in the rabbits of group 2, which were treated with streptomycin alone. The only evidence of activity found in any of these eyes consisted in minimal infiltration with wandering cells in the iris and corneal stroma. The persistence of wandering cells in the stroma of the cornea, iris and ciliary body can scarcely be considered evidence of an active tuberculosis in eyes which two months previously had been the site of active disease. It is probable that they are only the residua of the infection. There were many healed and encapsulated tubercles and no active ones. In the main, the tissue of the anterior ocular segment appeared essentially normal, and there were no lesions in the posterior segment.

Figure 6 *C* shows the cornea of rabbit 35, with minimal scarring still visible. Figure *D* shows a healed tubercle at the tip of the iris in the same rabbit.

Figure 7 *A* shows a low power view of the anterior segment of rabbit 37, with an essentially normal-appearing cornea and iris; *B*, the root of the iris in the same rabbit, with definite scarring in the iris and a few wandering cells throughout the stroma, and *C*, another section of the same iris with a few wandering cells. The persistence of wandering cells in the stroma of the cornea, iris and ciliary body can scarcely be considered evidence of active tuberculosis in eyes which two months previously had been the site of active disease. It is probable that they are only the residua of the infection. No definitely active lesions could be seen in the eyes of the rabbits of group 3.

Transmission Experiments.—On April 27 and 28, 6 animals from each group were killed for trasmission experiments. The diseased eyes were removed and the uveal tracts dissected out, and a saline extract of the tissue was prepared, as previously described, and inoculated into the anterior chambers of the eyes of normal rabbits. The results of these experiments were as follows:

GROUP 1: In the eyes of all the normal rabbits inoculated with extracts of the uveal tissue of the untreated controls a frank, outspoken ocular tuberculosis had developed by May 18. The incubation period ranged from fourteen to twenty-one days. The ocular tuberculosis ran the usual course of the disease in normal rabbits, and the tuberculous nature of the inflammation was confirmed by histologic examination of the eyes.

GROUP 2: In 3 of the transfer rabbits frank, typical ocular tuberculosis developed in the inoculated eyes. The incubation times were, respectively, sixteen, thirty-one and thirty-one days, with an average of twenty-six days. After development of activity, the disease ran the usual course of ocular tuberculosis in the normal rabbit. The inoculated eyes of the other 3 rabbits remained normal during the period of observation (up to June 19). Thus, the extracts of the uveal tissue from 50 per cent of these rabbits were noninfectious on subinoculation.

GROUP 3: In 3 of the transfer rabbits ocular tuberculosis developed in the inoculated eyes. The incubation periods were twenty-four, thirty-eight and thirty-eight days, respectively, with an average of thirty-three days. The eyes of the other 3 transfer rabbits remained normal during the entire period of observation (eight weeks), the transfer material being noninfectious.

The finding that 50 per cent of the treated animals in groups 2 and 3 had infectious uveal tracts is in contrast with the result in a previously reported experiment in which immune-allergic rabbits with ocular tuberculosis were treated with "promin" or "promizole" alone. In this experiment only 1 of 7 of the transferred uveal extracts was infectious. This discrepancy is probably accounted for by the different technic used in the preparation of the uveal extract. In the transfers from rabbits treated with "promin" or "promizole," the uveal tracts were macerated in a mortar with sand and 5 cc. of saline solution. The greater amount of diluent used in these previous transfers probably accounts for the lower incidence of positive results.

Cultures.—After the extracts of uveal tissue from the three groups had been prepared, each extract was cultured on Petragnini medium immediately before the ocular inoculations were made in the transfer rabbits. The results of these cultures were as follows:

GROUP 1: All cultures from the untreated controls were positive. Colonies were noted as early as the second week, and many colonies were macroscopically visible at the end of four weeks. At the end of eight weeks the slants of these 6 cultures showed the following number of colonies: 15, 30, innumerable, 11, 28 and 16. Microscopic examination of these colonies, stained for acid-fast organisms, showed pure cultures of tubercle bacilli.

GROUP 2: Three of the 6 cultures were positive for tubercle bacilli and 3 were negative. The growth, however, was exceedingly scanty. On 2 of the positive cultures there was only one colony, and on the third, only two colonies. These colonies were first detected on June 1, five weeks after inoculation. The transfer rabbits inoculated with 2 of the positive cultures showed ocular tuberculosis, while the third transfer rabbit, inoculated with an extract which showed only one colony, did not have the disease. Smears from these 3 positive tubes showed pure cultures of tubercle bacilli. Smears from the negative tubes showed no organisms.

GROUP 3: There was no macroscopic growth of any kind on any of the 6 cultures. Smears were made from all tubes and stained for tubercle bacilli by the usual technic for acid-fast organisms. Five of these smears were negative for the organisms. The sixth smear showed an occasional tubercle bacillus, despite the fact that there were no macroscopic colonies.

The bacilli recovered from the rabbits of group 2 were then tested for their sensitivity to streptomycin, to determine whether any resistance had been developed by the organism through treatment with streptomycin. The results of these studies of sensitivity will be reported later.

Recurrences.—After the completion of treatment, on April 26, 9 rabbits from group 1, 8 rabbits from group 2 and 9 rabbits from group 3 remained after their companions had been killed for histologic study and transmission experiments. These animals were kept under observation for a further period of eight weeks without treatment, to observe whether any relapses occurred in the eyes of the treated rabbits after cessation of treatment.

The disease in the rabbits of group 1 ran the usual course, with gradually waning activity, so that, on June 19, 7 of the 9 had no clinical activity, while the remaining 2 showed an average activity of 1.0.

Of the rabbits of group 2, which were treated with streptomycin alone, 3 had relapses. In 1 of these (rabbit 16) the relapse occurred on May 4, one week after cessation of treatment, and in the other 2 (rabbits 52 and 53), on May 11, two weeks after cessation of treatment, the average period of remission being twelve days. All these eyes with a relapse of the disease continued to show moderate activity during the period of observation, up to June 19. On this date the degrees of activity were, respectively, 0.5, 1 and 2. Three rabbits in this group died within one month after cessation of treatment. Unfortunately, these animals died over a weekend, and the bodies were discarded without a general autopsy, the eyes alone being removed for section. Up to the time of death, there had been no ocular exacerbations in these rabbits. Histologic examination of the enucleated eyes

showed only the same minimum to moderate degree of tuberculous activity noted in the eyes of the other rabbits treated with streptomycin alone.

None of the rabbits of group 3 had relapses until June 1, thirty-four days after cessation of treatment. On this date, 1 rabbit showed a slight trace of recurring inflammation, which persisted, without progression, during the remaining three weeks of observation.

A summary of the observations on transmission experiments, cultures and recurrences are shown in the accompanying table.

COMMENT

These results speak for themselves. Streptomycin alone has a strongly deterrent action on ocular tuberculosis in the "immune-allergic"

Summary of Observations on Transmission Experiments, Cultures and Recurrences in Rabbits with Ocular Tuberculosis Treated with Streptomycin and/or "Promizole"

	Transfer Experiments		Cultures of Uveal Extracts		Recurrences	
	Results	Incubation Period, Days	Results	Incubation Period	Results	Period of Remission, Days
Group 1 (untreated controls)	100% positive	17	100% positive for tubercle bacilli	Heavy growth in 4 weeks	Gradually waning activity	
Group 2 (streptomycin alone)	50% (3) positive; 50% (3) noninfectious	26	50% (3) positive for tubercle bacilli; 50% (3) negative	1-2 colonies in 5 weeks	3 out of 8 (37%)	12 (average)
Group 3 (streptomycin and "promizole")	50% (3) positive; 50% (3) noninfectious	33	83% (5) negative; 17% (1) positive	Microscopic growth in one culture only in 8 weeks	1 out of 9 (11%) (minimum reaction)	34

rabbit, but clearly, under the conditions of this experiment, in the doses given over the period of treatment, did not exert a completely bactericidal action on the tubercle bacilli in the sense that the bacilli were uniformly destroyed in all animals. Despite the appearance of complete clinical inactivity, there remained minimal to moderate microscopic evidences of tuberculous activity in all the eyes examined histologically. After cessation of treatment, the disease in the eyes of 3 rabbits treated with streptomycin alone relapsed rather promptly and continued to smolder over a six or seven week period of observation. The extracts of uveal tissue from 3 eyes of the rabbits treated with streptomycin alone were infectious, while those from the other 3 were noninfectious. Three of the cultures of these uveal extracts were positive for tubercle bacilli. Thus, while streptomycin alone produced pronounced clinical improvement, it could not be called a "cure" for ocular tuberculosis.

Histologic examination of the eyes of the rabbits treated with streptomycin alone indicated a strong bacteriostatic, but certainly very incomplete, bactericidal action on the tubercle bacilli. That such a bacteriostatic action and incomplete bactericidal action exist was confirmed by the fact that after cessation of treatment there were recurrences in 3 of the 8 surviving rabbits of this group. That there was some bactericidal action, however, is indicated by the fact that in 3 of the transfer rabbits the disease did not develop, the inoculated uveal extracts being noninfectious, and also by the fact that the cultures of these extracts were negative for the bacilli in 3 instances, while the 3 positive cultures showed only one or two colonies. This is in contrast with the results for the control group, in which transfer material gave positive results in 100 per cent of the experiments and the uveal tissue extracts yielded from 11 to innumerable colonies on culture.

When streptomycin and "promizole" were used together, the effect on the clinical course of the disease was greater than when either agent was used separately. The difference in the histologic picture was most striking, there being practically no microscopic evidence of any active tuberculosis in any of the rabbits treated with the combination of the two agents. From the histologic picture alone, one could well conceive of a complete bactericidal action on the tubercle bacilli. Such a complete action, however, was not confirmed by the transmission experiments, by the cultures of the uveal tissue extract or by recurrences in the survivors. In the transmission experiments, the results were somewhat similar to those in which the transfer material was from rabbits treated with streptomycin alone—there were 3 positive transfers in 6 experiments. The incubation period was, however, somewhat longer, thirty-three as against twenty-six days. There was a difference also in the results of culture of the uveal tissue extracts, the cultures of the tissue extracts of the rabbits treated with streptomycin and "promizole" yielding no tubercle bacilli in 5 instances, while the sixth culture showed only a microscopic growth. The results indicate that few viable bacilli must have remained in the uveal tracts of these rabbits. Further, there was only 1 recurrence in the 9 survivors of group 3. It seems fair, therefore, to postulate that, under the conditions of this experiment, the combination of streptomycin and "promizole" exerted a strong bactericidal action against the tubercle bacilli, in addition to the bacteriostatic action. From this accumulated evidence, it is a logical deduction that had the streptomycin-"promizole" treatment been continued longer, a complete bactericidal action might have been attained.

Since "promizole" is nontoxic, and can apparently be given indefinitely to both animals and man, these experiments suggest further that if the clinical disease can be controlled by combined treatment with

streptomycin and "promizole," the more toxic streptomycin might be discontinued and the administration of "promizole" continued until either complete bactericidal action or encapsulation of the lesions has taken place.

SUMMARY AND CONCLUSIONS

Streptomycin exerted a deterrent action on the course of ocular tuberculosis produced by inoculation of the eyes of immune-allergic rabbits. The improvement in the clinical picture was noted after nine days of treatment and was definite in sixteen days. After four weeks of treatment, the disease was clinically inactive in 15 of 20 rabbits, and after eight weeks of treatment it was clinically inactive in all.

Despite the absence of clinical evidences of activity, histologic examination of the eyes of these rabbits showed minimal to moderate degrees of tuberculous activity. In transmission experiments, 3 of 6 rabbits showed infectious uveal tracts in the diseased eyes, and cultures of extracts of these tissues yielded tubercle bacilli in 3 instances. After cessation of treatment, active exacerbation of the tuberculosis occurred in 3 of 8 rabbits under continued observation.

The combination of streptomycin and "promizole" in the treatment of similar ocular tuberculosis in immune-allergic rabbits produced a more dramatic therapeutic response than was obtained with streptomycin alone. After four weeks of treatment, the disease in all 21 rabbits so treated appeared clinically inactive and so remained throughout the period of treatment. Histologic examination of the eyes of these rabbits failed to show evidence of any active tuberculosis, the tissues appearing normal and showing healed tubercles or, at the worst, the persistence of wandering cells in the stroma. However, after cessation of treatment, there was a relapse in 1 rabbit after a further period of thirty-four days, and in transmission experiments the extracts of the uveal tracts from the diseased eyes were infectious in 3 rabbits. The incubation period was definitely longer than that for the control transfers. Cultures of the uveal extracts were negative for tubercle bacilli in 5 instances and showed only a microscopic growth in the remaining culture.

The findings indicate that streptomycin has a definite bacteriostatic and a partial bactericidal action against the tubercle bacillus in ocular tuberculosis. The combination of streptomycin and "promizole" has a more pronounced clinical and a decidedly greater bactericidal action than has either agent used separately.

The therapeutic and the bactericidal action obtained from the combination of streptomycin and "promizole" appears somewhat greater than would be expected from a summation of their individual actions.

Johns Hopkins Hospital.

ABSTRACT OF DISCUSSION

DR. PHILLIPS THYGESON, San Jose, Calif.: The difficulties encountered in clinical therapeutic research in ocular tuberculosis are serious but, when interpreted in the light of preliminary animal studies, are not insurmountable. Studies on human subjects are limited by many factors: 1. There is the difficulty in making a certain diagnosis of the disease—as a matter of fact, the diagnosis must always be presumptive, even in cases of frank granulomatous uveitis. 2. The series is necessarily small unless cooperative studies in several institutions can be undertaken. 3. Variability in the clinical course of human ocular tuberculosis makes necessary a large series for reliable interpretation of results. 4. It is impossible to control human results by histologic or cultural methods, as can be done in animal experiments. For these reasons, I look on the present study as being far more significant than the usual type of limited clinical therapeutic study of ocular tuberculosis.

When I was in Baltimore recently, I had the opportunity of examining with Dr. Woods representative animals from each of the three groups. The contrast between the gross appearance of the eyes in the control group and that of the eyes in group 3 was striking. I was especially impressed by the histologic evidence of differences between these two groups, which was clearcut and unmistakable. Dr. Woods has ample evidence to support his conclusion that "promizole" combined with streptomycin exerts a definite, if not complete, bactericidal action on the tubercle bacillus in the rabbit eye, and that the combination is superior to streptomycin alone.

These experiments would seem to be a guide to further therapeutic studies of ocular tuberculosis, since it is inevitable that chemotherapeutic agents more active than "promizole" and antibiotics more active than streptomycin will be developed in the future. I am informed that a considerably more active antibiotic, known as "aureomycin," is already in production. It seems to me that human therapeutic studies can now be undertaken with much more confidence and their results interpreted in the light of experience with these more exact animal studies.

I hope that the authors will offer a few words of recommendation to those of us who have begun human therapeutic studies with streptomycin and other agents, and I should like to ask whether they think that cooperative studies might be feasible in some of the larger cities. I have in mind the situation in San Francisco, where a program and clinic for the study and treatment of uveitis has been established at the University of California and patients are received from over the entire Bay area. It is conceivable that all patients with this disease, at least of clinic status, might be channeled to one institution, which could thus carry on extensive therapeutic studies with a sufficiently large series.

The problem of ocular tuberculosis, while not so important as it was twenty years ago, is still a major one, and it would seem from Dr. Woods's results that there is real hope of controlling this serious disease.

DR. JOHN G. BELLOWS, Chicago: This excellent report is a continuation of the brilliant investigations which have added so much to knowledge of ocular tuberculosis.

This paper is important, for it destroys the old idea that ocular tuberculosis is basically any different from other infectious diseases of the eye. Although ocular tuberculosis differs from other infections

of the eye in many respects, it is essentially similar; of particular importance is the fact that it responds favorably to chemotherapeutic and antibiotic agents.

This paper demonstrates the value of the synergistic, or additive, action obtainable by using antibiotics in combination with chemotherapeutic agents and drugs. It has been shown that the effect of penicillin combined with the sulfonamide compounds, or of streptomycin with penicillin and the sulfonamide drugs, was far superior to the effect which might have been expected from each drug given separately.

The importance of early treatment has been stressed. At Northwestern University, Dr. Farmer and I have also demonstrated that streptomycin must be employed early in order to be effective in experimental and clinical infections of the eye. For example, infections of the vitreous produced by inoculating a virulent strain of streptococci can be prevented if streptomycin is injected intraocularly within twelve hours. If given later, it has little effect on the course of the infection.

While one cannot carry over the results from experimental animals to clinical cases without many reservations, we have reason to expect from Dr. Woods's experiments that effective results may be possible from the synergistic, or additive, effect of streptomycin and "promizole" given in smaller doses than would be employed when either agent is used alone. This reduces the chances of producing the toxic manifestations of both the antibiotic and the sulfone.

DR. ALAN WOODS, Baltimore: I should like to thank Dr. Bellows for his suggestion about the possible basic action of the sulfonamide drugs. It had not occurred to me. Dr. Thygeson brings up the fascinating question of the clinical use of these preparations and asks for certain information. The difficulty in their clinical use is based on two fallacies: 1. The diagnosis of ocular tuberculosis, as Dr. Thygeson said, is a presumptive one, and is usually about as good as the individual physician's experience with ocular tuberculosis. The validity of the diagnosis is also in proportion to his diagnostic equipment—his ability to rule out various factors. 2. The evaluation of the treatment is simply the personal opinion of the observer that the eye responded more quickly than would otherwise have been expected. Thus, the clinical therapeutic experiment is totally uncontrolled. The experiments I have presented are controlled; we can evaluate every factor. Therefore I think that in the clinical use of streptomycin and "promizole" in treatment of ocular tuberculosis it is necessary in the beginning to limit the use of the therapy to a condition so frankly ocular tuberculosis that there could be little doubt as to the diagnosis. Second, as to the dosage of streptomycin, there have been a number of interesting studies, largely from the Veterans Administration and the Fourth Streptomycin Conference. These studies indicate that people do just as well on 0.5 Gm. of streptomycin given twice a day as they do on 2 or 3 Gm. a day; in fact, the drug may be given only once a day, or every second day, with almost equally good effects. We have treated a number of patients with clinical ocular tuberculosis. The results must be the subject of another report when sufficient material is accumulated and when conclusions appear valid enough. We have given 0.5 Gm. of streptomycin intramuscularly twice a day. This dose would theoretically produce minor involvement of the vestibular nerve in a small percentage of cases. We

have had no trouble yet on this score with such a dose. Streptomycin has been given with the idea of continuing its administration until the patient has received a total of 100 or 125 Gm.; this represents about three months' treatment. "Promizole" can be given safely up to about 6 Gm. a day, 1.5 Gm. being given in four doses throughout the day. The total daily dose has sometimes reached 12 or 14 Gm. I am not now specifically recommending this form of treatment; I am only trying to answer Dr. Thygeson's question. I am afraid one might get into trouble if such treatment were used promiscuously. Because the physician's evaluation is about as good as his experience, I should like to see the use of these preparations limited, at first, to frank cases of ocular tuberculosis. I believe antibiotic and sulfonamide therapy has definite promise for this disease. I quite agree that better antibiotics will be found, and likewise better sulfonamide compounds. Others are now available. However, it takes about a year to carry out a study on one of these drugs and to evaluate the treatment in experimental animals.

I trust, therefore, that, if the treatment is used, it will be confined to cases in which there can be little, or no, question of the diagnosis and in which the outcome can be fairly well evaluated by an experienced ophthalmologist.

RETINAL TUMOR ASSOCIATED WITH NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

Report of a Case

FRITZ J. BLOCH, M.D.
NEW YORK

IN 1882 von Recklinghausen [1] described a disease which he called neurofibromatosis. The disease is usually familial, showing mendelian dominance in successive generations, although occasionally skipping a generation. There is no sign of sex-linked inheritance. The disorder is characterized by cutaneous pigmentation and multiple tumors of the cranial and peripheral nerves. In some cases neurofibromatosis is associated with involvement of the skeleton and with disturbances of the glands of internal secretion and mental disorders, including epilepsy. The skin may show a uniform bronzing of various parts. The most typical cutaneous lesions are the circular or oval patches, with sharply defined edges, observed on the trunk. Nevoid formations are frequent.

An ocular complication described by Michel [2] (1873) before the syndrome itself was known was a tumor of the optic nerve in a girl with elephantiasis neuromatodes, a form of neurofibromatosis. At present the ocular complications of neurofibromatosis are classified in three sharply separated groups, each presenting interesting features and problems.

1. Tumors of the ocular adnexa and external coats of the eye. There may be hyperplasia and hypertrophy of the skin of the eyelids and the neighboring temporal and facial regions to a degree suggesting elephantiasis. Large or small, single or multiple tumors of the eyelids and the supraciliary region may be seen, as well as tumors of the palpebral and bulbar conjunctiva and of the cornea. Ptosis may be present. In 1945 Allende [3] reviewed the literature and reported an additional case of conjunctival tumor associated with neurofibromatosis.

From the service of Dr. E. B. Gresser, Department of Ophthalmology, Beth Israel Hospital.

1. von Recklinghausen, W.: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen, Rudolf Virchow Festschrift, Berlin, 1882.

2. Michel, J.: Ueber eine Hyperplasie des Chiasma und des rechten n. opt. bei Elephantiasis, Arch. Ophth. **19**:145, 1873.

3. Allende, F. P.: Diffuse Neurofibromatosis (von Recklinghausen's Disease) Involving the Bulbar Conjunctiva, Arch. Ophth. **33**:110 (Feb.) 1945.

2. Defects of the bony structure of the orbit, causing pulsation of the eyeball. Dehiscences in the orbital roof allow free communication between the orbit and the intracranial cavity. Exophthalmos, which is frequently found with these orbital defects, may be caused either by orbital tumor formation or by herniation of brain tissue into the orbit. Pulsation of the eyeball is synchronous with the radial pulse. It is unaccompanied with bruit, and the patient is not annoyed by the condition. It was first reported by Rothcliffe and Parsons,[4] but received little attention until 1931, when Moore [5] reported 4 cases. In 1936 Wheeler [6] analyzed the condition and added 5 cases. Recently a review of the 20 reported cases, with the addition of 5 of their own, has been published by Peyton and Simmons.[7]

3. Intraocular tumors. For practical reasons, these may be subdivided into three groups. (*a*) Tumors of the uveal tract. They are especially interesting as a frequent cause of buphthalmos. Since Schiess-Gemuseus [8] (1884) described the first case, 33 such cases have been recorded in the literature. The most recent and thorough analysis is that of Anderson.[9] (*b*) Tumors of the optic nerve head. The first instance of a relation between ocular complications and neurofibromatosis is that of a tumor of the optic nerve head reported by Michel, as previously noted.[2] In 1940 Davis [10] tabulated 33 cases from the literature and added 5 cases of his own, all associated with neurofibromatosis. He suspected that other cases of reduced vision and optic nerve atrophy fall within this classification. (*c*) Tumors of the retina. This complication is extremely rare. Van der Hoeve,[11] in his painstaking researches on tuberous sclerosis, became convinced that this disease is closely related to neurofibromatosis, and he made ophthalmoscopic examinations in a great number of cases of these diseases. He was able to find retinal changes in 3 patients with neurofibromatosis. The first was a man aged 33 with bilateral tumor of the acoustic nerve and cutaneous lesions.

4. Rothcliffe, W. C., and Parsons, J. H.: Plexiform Neuroma of the Orbit, Tr. Path. Soc., London **55**:27, 1913.

5. Moore, R. F.: Diffuse Neurofibromatosis with Proptosis, Brit. J. Ophth. **15**:272, 1931.

6. Wheeler, J. M.: Pulsation of the Eyeball Associated with Defects in the Wall of the Orbit, Bull. Neurol. Inst. New York **5**:476, 1936.

7. Peyton, W. T., and Simmons, D. R.: Neurofibromatosis with Defect in Wall of Orbit, Arch. Neurol. & Psychiat. **55**:248 (March) 1946.

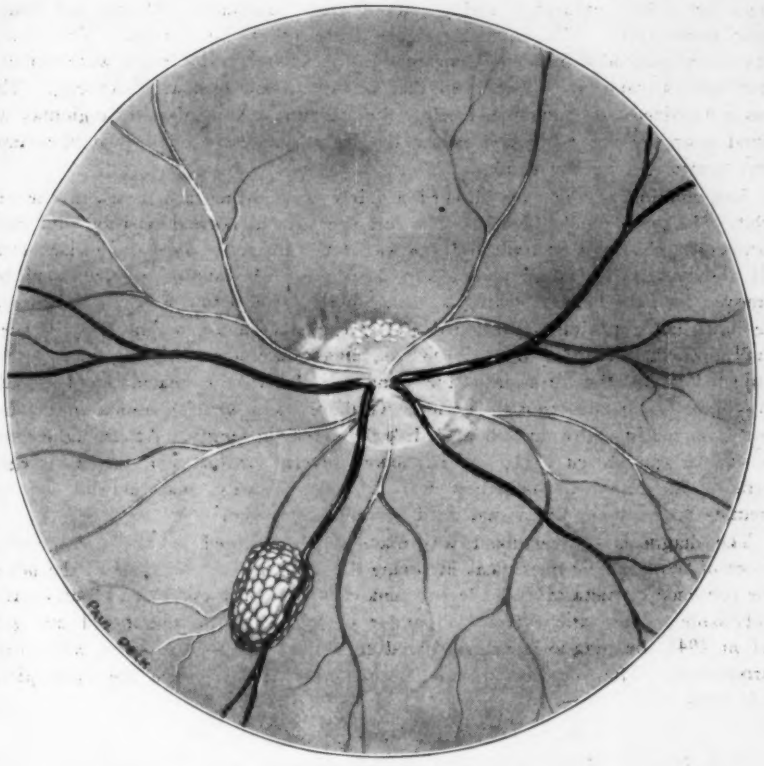
8. Schiess-Gemuseus: Vier Fälle angeborener Anomalie des Auges, Arch. f. Ophth. **30**:191, 1884.

9. Anderson, J. R.: Hydrophthalmia or Congenital Glaucoma, London, Cambridge University Press, 1939.

10. Davis, F. A.: Primary Tumors of the Optic Nerve: A Phenomenon of Recklinghausen's Disease, Arch. Ophth. **23**:734 (April) 1940.

11. van der Hoeve, J.: Eye Diseases in Tuberous Sclerosis of the Brain and in Recklinghausen's Disease, Tr. Ophth. Soc. U. Kingdom **43**:534, 1923.

In the macula of the left eye a small yellowish lesion and, below that, a grayish one were observed. Temporal to the nerve head was a grayish, umbilicated tumor. Another tumor was seen nasally and above between two vessels. The second patient presented a great number of grayish white tumors in each fundus. The third showed bilateral optic nerve atrophy and in the right eye several small tumors of the retina. The tumors closely resembled those seen in tuberous sclerosis. In 1938 Stallard [12] described the case of a youth aged 19 whose left eye showed



Fundus showing retinal tumor associated with neurofibromatosis.

a hemispherical, grayish mass protruding from the nerve head. The pathologic examination of the enucleated eye showed that the tumor had invaded all the layers of the retina and the advancing edge had wedged itself laterally between the nuclear layers. Whether the tumor in this case may be counted as an actual retinal tumor is doubtful. An additional case is reported from my experience.

12. Stallard, H. B.: A Case of Intraocular Neuroma (von Recklinghausen's Disease) of the Left Optic Nervehead, Brit. J. Ophth. **22**:11, 1938.

REPORT OF CASE

S. R., a man aged 69, Jewish, sought advice from the clinic of Beth Israel Hospital on Feb. 8, 1938, because of pains in his legs. His low intelligence made the taking of an exact history difficult, but it was established that he was a widower with a healthy grown son and that his wife had not had any miscarriages or stillbirths. In 1915 a preliminary iridectomy had been performed on each eye. By 1927 the right eye was in a state of absolute glaucoma and was subsequently removed. Unfortunately, all previous records and specimens were lost.

Physical examination showed a slightly obese man, 5 feet 3 inches (160 cm.) in height and weighing 160 pounds (72.6 Kg.). The urine contained 110 mg. of sugar per cubic centimeter, and the blood sugar measured 190 mg. per hundred cubic centimeters. The internal organs were otherwise normal. The diabetes was easily controlled by diet. Beneath the skin around both elbows were numerous firm tumors, ranging in size from that of an almond to that of an egg. There was a fist-sized, soft tumor just below the sternum. Almond-sized angiomas were found near the upper lip and below the right scapula. Small, wartlike tumors were scattered over the trunk.

Examination of the eyes showed a fairly well fitting prosthesis in the right orbit. No tumor could be felt. The left eye was in normal position and moved normally. The conjunctiva and cornea were normal. The otherwise normal iris showed a surgical coloboma at 12 o'clock. A cataractous lens had been removed intracapsularly, leaving a clear pupil. The optic nerve was white, and the nasal margin slightly scalloped and irregularly raised, as in the presence of small drusen. At 12 and at 7 o'clock, finger-like areas of choroidal atrophy projected from the disk into the fundus. Below the macula and about 4 disk diameters distant from the optic nerve there was a grayish tumor, measuring 1 disk diameter in width and about 3 disk diameters in length. At its highest point its surface was raised 1 D., and it showed several whitish spots on its irregular surface. Vision with correction was 20/100. Tension was normal. Several attempts to evaluate the visual field were unsuccessful.

The diagnosis of melanoma was made and confirmed by the roentgenologic report of "osteoplastic metastasis involving the skull and the left side of the pelvis." The presence of metastases made the removal of an only eye in an elderly patient inadvisable. The patient remained under observation; the tumor did not grow, and in 1941 the diagnosis was changed to retinal tumor associated with neurofibromatosis. The last examination, in February 1947, showed the same picture as in 1938.

COMMENT

The retinal tumor observed in this case of neurofibromatosis shows the same ophthalmoscopic picture as that of tumors seen in tuberous sclerosis. Whether the two diseases are identical is questionable, but a relationship has been suggested. As early as 1912, long before the retinal changes in either disease were known, Orzechowski and Novicki [13] drew such a conclusion from their pathologic studies. Van der Hoeve,[14]

13. Orzechowski, K., and Novicki, W.: Zur Pathogenese and pathologischer Anatomie der multiplen Neurofibromatose und der Sklerosis tuberosa (Neurofibromatosis universalis), Ztschr. f. d. ges. Neurol. & Psychiat. **11**:237, 1912.

14. van der Hoeve, J.: Eye Diseases in Tuberose Sclerosis of the Brain and in Recklinghausen's Disease, Tr. Ophth. Soc. U. Kingdom **43**:534, 1932; footnote 11.

who studied the condition most extensively from the ophthalmologic viewpoint, expressed the belief that tuberous sclerosis is closely related to Recklinghausen's neurofibromatosis, von Hippel–Lindau angiomatosis and the Sturge-Weber syndrome. The common point in these syndromes is the combination of cutaneous lesions with a tendency to form tumors in the most varied parts of the body, including the eye. He called the whole group phakomatosis, from the Greek word φακός for lentil, or mother spot. As long as the cause of these diseases is unknown and pathologists disagree about the nature and structure of the tumors, this is an excellent working hypothesis, and one cannot accumulate too much clinical and pathologic material to help in clarifying the situation. The importance of a thorough knowledge of these conditions in the everyday practice of ophthalmology is illustrated by our case, in which only a chain of circumstances saved the patient's eye from well intended, but unnecessary, enucleation.

SUMMARY

A retinal tumor in a case of neurofibromatosis (Recklinghausen's disease) is reported. The tumor is ophthalmoscopically identical with tumors commonly seen with tuberous sclerosis. In nine years of observation the fundus picture has not changed.

VISION IN STRABISMUS

A Preliminary Report

FRANK COSTENBADER, M.D.

DOROTHY BAIR, B.A.

AND

ALICE McPHAIL, R.N.

WASHINGTON, D. C.

MUCH has been written about the effect of strabismus on vision, and since the time of Claude Worth [1] poor vision as a result of disuse in strabismus has been increasingly recognized. Since this time, also, less emphasis has been placed on the effect of vision on strabismus. It is our purpose to point out certain things in the relationship of vision and squint.

Little need be said about the fact of amblyopia ex anopsia. It is now well established that most visual defects associated with squint are the result of the squinting and subsequent disuse of the affected eye. Prior to Worth it was generally felt that there was much organic visual defect—congenital amblyopia—and that the squint resulted from the poor vision. In this paper, a portion of our file of private cases of strabismus will be analyzed. The factors in determination of vision in children will be commented on. The factors in the causation of amblyopia ex anopsia, as well as those factors which influence the treatment of amblyopia, will be discussed. The types and specific application of the various forms of treatment will be considered. Further, the association of organic ocular defect and strabismus will be commented on. It is not intended that this study should be exhaustive or conclusive; rather, it is felt that attention shall be drawn again to "how seeing affects squint" and "how squint affects seeing."

REVIEW OF THE LITERATURE

Brief reference to the literature reveals certain facts. Chavasse [2] graphed visual development in the child, showing that vision of 6/12 is normal for the 2 year old child and that vision matures gradually

Read at a meeting of the Detroit Ophthalmological Society, Feb. 28, 1947, and the Washington, D. C., Ophthalmological Society, March 4, 1947.

1. Worth, C.: Squint, ed. 6, Philadelphia, P. Blakiston's Son & Co., 1929.

2. Chavasse, B. F.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1940, chap. 26.

until, at the age of 5 years, normal vision of 6/7 is attained. It is recognized, however, that in some children vision of 6/6 is attained by the age of 4 years, and in others not until the age of 8, in eyes which are structurally normal.

Vision in the small child can best be determined by his ability in foveal fixation. Peter,[3] Worth [1] and Bielschowsky [4] agreed that foveal fixation is quickly lost in the infant and is quickly regained, and that the older child loses fixation more slowly and regains it more slowly. Whereas Worth [1] stated that foveal fixation cannot be regained after the sixth year of life, Bielschowsky [4] cited cases of adults who had extremely poor vision in a squinting eye until the good eye had been lost by injury or disease; then foveal fixation was regained, and in a few cases good vision was restored. Yoxall [5] cited 42 cases of patients, ranging in age from infancy to 11 years, all of whom regained foveal fixation and good vision on total occlusion for periods up to twenty-eight months. While the wisdom of such prolonged occlusion may be questioned, the final good vision seems justification in itself. No reference has been found to an attempt to correlate the ability in foveal fixation with an accurate estimate of visual acuity.

The fact of suppression as a forerunner to amblyopia ex anopsia is well established by the writings of Peter,[3] Travers,[6] Bielschowsky,[4] Enos,[7] Sugar [8] and others. Peter expressed the belief that the scotoma of suppression is only 2 to 3 degrees in diameter, while Travers and others mapped much larger scotomas. There are two scotomas in many cases of squint: the first, the area of the squinting eye which corresponds to the visual direction of the fovea of the fixing eye; the second, the area involving the macula of the squinting eye, and that only in cases of monocular squint. This is the forerunner of amblyopia ex anopsia (Travers [6]). Sugar [8] suggested the term "suppression amblyopia" as a better term than amblyopia ex anopsia. Enos [7] found that, while amblyopia is commonest with esotropia, suppression alone is commonest with exotropia.

Amblyopia ex anopsia, now recognized since its definition by Worth [1] in 1903, raises many questions. Bielschowsky [4] asked why some persons

3. Peter, L. C.: Extraocular Muscles, ed. 2, Philadelphia, Lea & Febiger, 1936.

4. Bielschowsky, A.: Lectures on Motor Anomalies, Hanover, N. H., Dartmouth College Publications, 1940.

5. Yoxall, I.: Loss of Central Fixation, Brit. Orthoptic J. **1**:15, 1939.

6. Travers, T. a'B.: Concomitant Strabismus, Brit. J. Ophth. **20**:407, 1936.

7. Enos, M. V.: Suppression and Amblyopia, Am. J. Ophth. **27**:1266 (Nov.) 1944.

8. Sugar, H. S.: Suppression Amblyopia, Am. J. Ophth. **27**:851 (May) 1942.

with squint retain and others lose vision, and why the reduced vision is maintained indefinitely in spite of further disuse. Chavasse [2] stated that nearly 50 per cent of persons with esotropia are anisometropic and that the amblyopia varies directly with the anisometropia. He further classified amblyopia as of four grades, in two of which fixation is lost and even light projection is questionable, especially in the temporal field. In the third grade, eccentric fixation is present, and in the fourth foveal fixation and visual acuity up to 6/6 may be found. Feldman and Taylor [9] stated that ametropia is no great factor in causing amblyopia and that the higher refractive errors do not make the amblyopia harder to cure. Morgan [10] reported 77 cases of amblyopia in the Army, in 56 per cent of which it was associated with squint and presumably could have been prevented. Anisometropia was the cause in 30 per cent, and amblyopia without obvious cause was present in 14 per cent.

All authors, in discussing amblyopia ex anopsia, have emphasized the necessity of early treatment. Treatment consists primarily in occlusion. Morgan [10] cited Zimmerman as stating that 91 per cent of 68 patients obtained 20/20 + vision, while Yoxall [5] reported that prolonged occlusion led to 41 of 42 patients' regaining foveal fixation, and that 37 obtained equal vision in the two eyes after occlusion for periods up to twenty-eight months. Travers [6] stated that the prognosis depends on the age of the patient and the duration of squint. He cited Sattler, whose 89 patients obtained equal vision in two eyes—in children below 2 years in one to six weeks, in the 2 to 4 year group in one to three months and in the 8 to 12 year group in one to three years. He stated that a patient with amblyopia over 6 years of age with a vision of 6/60 or less has a poor prognosis. Worth [1] stated that the vision of 165 patients who had squinted less than one eighth of their lives improved to 6/6 on occlusion. Chavasse [2] stated that "expectation for sight for the amblyopic eye depends on the answer to two questions, 'How old was the patient when dissociation (failure of binocularity) began?' and 'How old is the patient now?' "

These references emphasize the uniformity of the acceptance of the origin of amblyopia from disuse, the necessity of early treatment for good results and the importance of total occlusion in order that the treatment be truly effective.

PRESENT STUDY

In the present survey are analyzed the data on 407 unselected private patients with squint, all of whom we examined. Throughout the analysis and discussion,

9. Feldman, J. B., and Taylor, A. F.: Obstacle to Squint Training: Amblyopia, Arch. Ophth. **27**:851 (May) 1942.

10. Morgan, G. E.: Amblyopia ex Anopsia in the Army, Am. J. Ophth. **29**: 713 (June) 1946.

emphasis is placed on the ways in which the squint affected the vision and how the vision may have affected the squint. Patients having organic ocular defects are considered separately and are not necessarily considered unacceptable for treatment. Information obtainable from the history is analyzed and correlated with the clinical findings. The visual acuity is correlated with other ocular findings, such as the type of squint, the amount of deviation and the refractive error. Methods of treatment of amblyopia are indicated.

In this survey, corrected vision of 20/40 or less is considered subnormal and is assumed to be due to amblyopia ex anopsia unless an organic lesion could be demonstrated. The child knowing his alphabet was tested with the Snellen letter chart, while the child from 4 to 7 years of age was tested with the E chart. Below the age of 4 years, or until such an age as the E chart could be used, "fixation" was used to estimate vision. "Picture" charts were not used at any time, since too much depends on the child's previous experience with the objects being pictured.

During a routine examination of a squinting patient, the ability to fixate with each eye separately was noted, and, when possible, an estimation of visual acuity on the letter or the E chart was obtained at the same time. With this procedure, estimates were obtained for 222 eyes. Three grades of fixation were used: grade 1, good and central; grade 2, poor but central (or unsteady but central), and grade 3, eccentric or roving.

Table 1 shows that 178 eyes had "good and central" fixation. On the Snellen chart the visual acuity ranged from 20/15 to 20/200, with an average of 20/34. Thirty-one eyes had "poor and central fixation," with a range in acuity of 20/30 to 4/200 and an average of 20/165. Thirteen eyes had "roving or eccentric" fixation, with a range of 20/200 to 3/200 and an average of 20/573. It must be admitted that too few eyes in the last two grades were examined, and the findings are only suggestive. None the less, the "average" visual acuities have been substituted in the survey for the corresponding ability to fixate.

TABLE 1.—*Estimation of Visual Acuity by Foveal Fixation*

Fixation	Number of Eyes	Average Visual Acuity	Range of Visual Acuity
Good and central.....	178	20/ 34	20/ 15 to 20/ 200
Poor but central.....	31	20/165	20/ 30 to 20/1,000
Eccentric; no fixation.....	13	20/573	20/200 to 20/1,400

Of 407 patients with squint (table 2), 316 had a convergent squint; and, of these, 132 (41.5 per cent) were amblyopic; 86 patients had a divergent squint, with 14 (16.2 per cent) amblyopic, and 45 patients had squint with a predominant vertical element, 20 (30.8 per cent) of whom were amblyopic. The total number of amblyopic patients was 143, or 35.1 per cent. It is readily apparent that esotropia is associated with the greatest number of amblyopic eyes and exotropia with the smallest number, with squint with a vertical element holding an intermediate position.

What help may be obtained from the history regarding the effect of the squint on vision in these 407 patients? It is recognized that a parent's estimate of the age of onset of the squint, its constancy and whether it is alternating or monocular is often not reliable, but may be of some help. Data on the following points in the history were noted: type of squint (periodic or constant, monocular or alternating), age of onset, duration of the squint, existence of squint among near relations and, finally, visual "confusion" associated with the squint.

Of 393 patients (table 3) a history of "periodicity" of the squint was obtained for 181; and, of these, 32 (17.7 per cent) were amblyopic.

TABLE 2.—*Type of Squint in Relation to Amblyopia*

	Number of Patients	Amblyopic Patients	
		Number	Percentage
Convergent	316	132	41.5
Divergent	86	14	16.2
Vertical component	45	20	30.8
Totals	407	143	35.1

TABLE 3.—*Relation of Vision to History of Squint*

	Number of Patients	Amblyopic Patients	
		Number	Percentage
Type			
Periodic	181	32	17.7
Constant	212	113	53.3
Alternating	105	14	13.3
Monocular	288	131	45.5
Age of onset			
Nonamblyopic patients	1 yr. 2 mo.		
Amblyopic patients	1 yr. 9 mo.		
Duration of squint			
Nonamblyopic patients	2 yr. 4 mo.		
Amblyopic patients	6 yr. 5 mo.		

The remainder, or 212 patients, had "constant" squint, 113 (53.3 per cent) of whom were amblyopic. "Alternating" squint was noted in the history of 105 patients, with 14 (13.3 per cent) amblyopic, while of 288 with a history of "monocular" squint, 131 (45.5 per cent) had an amblyopic eye. Again, although it is recognized that a parent's statement that a squint is "periodic" or is "alternating" may not be entirely true, the evidence is strongly in favor of finding a much lower percentage of cases of amblyopia among patients giving such a history and a much higher percentage among those giving a history of a "constant" or a monocular squint.

Again, the statement of age of onset may not be reliable. It is probable that in most cases the squint is present for weeks or months before the parents are cognizant of the fact, except possibly in cases of squint of acute or sudden onset. The present series seems to demonstrate (table 3) that the average age of onset of squint is earlier among nonamblyopic patients (1 year 2 months) than among amblyopic patients (1 year 9 months). These data are contrary to present teachings and common sense. It must be remembered that many nonamblyopic patients have congenital squint which alternates, thus giving an early average age of onset for this group. Correction for this factor places the age of onset for the two groups at about the same level.

More significant figures (table 3), however, demonstrate the importance of the "duration" of the squint, that is, the period from the onset (as obtained from the history) to the time of the beginning of treatment. The average duration of squint for the nonamblyopic group was two

TABLE 4.—*Vision in Relation to History of Visual Confusion and to Familial History of Squint*

	Number of Patients	Patients with History of Confusion	Amblyopic Patients	
			Number	Percentage
Confusion				
Divergence	50	34	4	10.5
Convergence	128	51	18	35.3
Family squint				
Nonamblyopic patients				46.2
Amblyopic patients				52.4

years and four months, while that for the amblyopic group was six years and five months. It becomes evident that while the age of onset may not be of great significance, the longer the squint exists, the oftener amblyopia is found, and probably the more deeply seated it is and the more difficult to cure.

The obtaining of accurate data concerning the incidence of squint in the patient's family is notably inaccurate. In our series an effort was made to determine the incidence of squint among immediate relatives of the patient. It will be noted (table 4) that 46.2 per cent of nonamblyopic squinters had squinting relatives, whereas 52.4 per cent of amblyopic squinters had squinting relatives. The difference for these two groups does not seen significant.

A final group of facts obtained from the history has been little stressed by other investigators. It was noted by us that in a high percentage of cases of exotropia in children the parents' chief complaint was that the patient constantly closed one eye when in the bright light, and at times when looking intently at objects of interest. This "sign"

became sufficiently frequent that a tentative diagnosis of divergence excess was made whenever the history of "closing one eye in the bright light" (especially summer sunlight) was obtained. It was assumed that, while form suppression was adequate in cases of divergence excess during divergence, light suppression was inadequate and confusion took place. Actually, the history of transitory diplopia is not infrequent in cases of divergence excess, an observation which suggests that in these cases even form suppression is incomplete.

Stimulated by these thoughts, we took a careful history of symptoms suggesting visual confusion. Such signs as closing one eye, true diplopia, rubbing one eye (in the absence of other causes) and excessive clumsiness were noted. In the histories of 50 patients with exotropia, confusion was noted for 34, only 4 of whom had amblyopia (table 4). Of 128 patients with esotropia, 51 gave evidence of visual confusion, 18 of whom were amblyopic. The inference is twofold. Visual confusion occurs much oftener in cases of exotropia, and amblyopia is less frequent when evidence of confusion is present. The "confusion" is evidence of incomplete suppression, and amblyopia is less likely to be present.

More accurate evidence of the relationship of squint and vision may be obtained from the ocular findings than from the history. It was believed that (1) the type of squint (e. g., "mechanical," as opposed to accommodative, squint, or alternating, as opposed to monocular, squint), (2) the minimal deviation (e. g., the least squint of which the patient was currently capable in any circumstances) and (3) the size and dissimilarity of refractive errors in the two eyes might affect the visual acuity, or have affected it prior to the beginning of treatment.

The 407 patients (table 5) included 316 with convergent squint, 41.5 per cent of whom had an amblyopic eye. A breakdown of this group into cases of mechanical, accommodative and combined convergent squint gives additional information. Of 108 patients with mechanical convergent squint, 47 (43.5 per cent) were amblyopic. An interesting subgroup is congenital mechanical squint (sometimes called "pseudoparesis of the lateral rectus muscles," "bilateral paresis of the lateral rectus muscles" or "congenital paralysis of divergence"). This type is characterized by isometropia, early weakness of abduction and a tendency to alternate. Because of its frequent alternating character, amblyopia developed in only 29.4 per cent.

The group of 98 patients with accommodative convergent squint (table 5) contained 32 (32.6 per cent) with amblyopia. Patients with this type of squint may be divided into those with the "typical" form (persons having hypermetropia, with obvious squint before wearing glasses but straight eyes for distance and near vision with glasses), and

those with the "atypical" form (persons with low hypermetropia, with straight eyes for distance both with and without correction, but pronounced convergence for near vision both with and without correction). Of the 26 patients with "typical" accommodation, who had less opportunity for straight eyes before treatment, 11 (42.3 per cent) had amblyopia, whereas of the 35 patients with "atypical" accommodation, having straight eyes for distance at all times, only 5 (14.3 per cent) had

TABLE 5.—*Vision and Other Ocular Findings*

	Number of Patients	Amblyopic Patients	
		Number	Percentage
Type of squint			
Convergent	316	132	41.5
Mechanical	108	47	43.5
Congenital	34	10	29.4
Accommodative	98	32	32.6
Typical	26	11	42.3
Atypical	35	5	14.3
Combined	105	50	47.6
Monocular	239	120	50.0
Alternating	62	5	8.1
Divergent	86	14	16.2
Divergence excess	42	7	16.2
Convergence insufficiency	5	2	40.0
Combined	39	5	12.8
Monocular	75	10	13.3
Alternating	1	0	0.0
Minimal deviation, D.			
0 - 5	193	41	21.3
5 +	214	102	47.7
Refractive error			
Hypermetropia, D.			
0 - 1	77	18	24.9
1 - 4	225	77	34.2
4 +	71	39	55.0
Myopia	6	3	50.0
Astigmatism (2 + D.)	41	28	68.3
Anisometropia, D.			
Less than 1	317	100	31.2
1 - 3	69	38	45.0
3 +	10	10	100.0

amblyopia. The cases are too few for a conclusive statement, but the inference is that the opportunity for binocular vision prevents amblyopia.

Of the 105 patients with "combined" convergent squint (some element of mechanical, as well as accommodative, convergence), 50 (47.6 per cent) had amblyopia (table 5). It is evident that in cases of convergent squint in which the eyes constantly are out of line amblyopia develops oftener than in the cases of periodic squint.

Also, it may be seen (table 5) that of 62 patients with "alternating" esotropia only 5 had any amblyopia (8.1 per cent). This diagnosis

was made at early visits, and at times amblyopia developed or became evident later. Of the 239 patients with monocular squint, 120 (50 per cent) had amblyopia, a figure corresponding closely to that for patients having a "history" of monocular squint.

Of 86 patients with exotropia (table 5), 14 (16.2 per cent) were amblyopic. Only 1 patient with alternating exotropia was found, the remainder being monocular. It should be recalled that many patients with divergence excess had "amblyopia," with a visual acuity of 20/25 or 20/30 +, but were not considered for this study.

In an effort to determine further the importance of the "opportunity for binocular vision" in inhibiting amblyopia, all patients were considered in the light of their minimal deviation. For instance, patients with divergence excess have straight eyes for near vision (a minimal deviation of zero), and patients with atypical accommodative convergent squint have straight eyes for distance (a minimal deviation of zero), whereas patients with mechanical and combined convergent squint never have straight eyes (a minimal deviation of 5 D. or more). Reference to table 5 shows that 193 patients had a minimal deviation of less than 5 D. and 41 (21.3 per cent) had amblyopia. The 214 patients with a minimal deviation of more than 5 D. included 102 (47.7 per cent) with amplyopia. It is then evident that the opportunity for binocular vision decreases the frequency of amblyopia.

A final correlation of interest is that of the state of the binocular refraction and its probable effect on corrected vision. It will be noted in table 5 that the hypermetropias have been subdivided into three groups on the basis of the size of the error. Myopia and excessive astigmatism are also indicated. The refraction of the eye having the larger error was used in each instance. Note that, contrary to the opinion of Feldman and Taylor,[9] who stated that ametropia is not a cause of amblyopia, the percentage of patients with amblyopia increased as the size of the hypermetropic error increased. Of 77 patients having an error of less than 1 D., 18 (24.9 per cent) were amblyopic, while of 225 patients having an error of from 1 to 4 D. 77 (34.2 per cent) were amblyopic and of 71 patients having an error of more than 4 D. 39 (55 per cent) were amblyopic. The increase in the percentage incidence of amblyopia as the hypermetropic correction increases is striking and rather conclusive.

Myopia occurred too infrequently (except as the congenital monocular and binocular types) to justify conclusions. Excessive astigmatism (over 2 D.) shows the highest percentage of patients with amblyopia (68.3 per cent), amblyopia occurring in 41 patients (table 5).

The role of anisometropia in the causation of amblyopia has been noted by numerous authors. In this study, it is evident that as the difference in the refractive error in the two eyes increases the percentage of cases

of amblyopia increases strikingly. Of 317 patients (table 5) having a difference of less than 1 D. in the two eyes, 100 (31.2 per cent) were amblyopic, whereas 38 of 69 patients (45 per cent) having a difference of 1 to 3 D. were amblyopic and all of 10 patients having a difference of 3 D. or more in the two eyes were amblyopic (100 per cent).

It is evident from consideration of the refractive errors of these patients with strabismus that as hypermetropia increases, or as anisometropia increases, amblyopia increases.

TREATMENT

Though numerous suggestions have been made concerning the treatment of amblyopia ex anopsia, the choice of effective procedures is limited. The purpose in such treatment is to force the use of the amblyopic eye, to create interest in such use and to encourage the patient in such activities by any methods possible.

When amblyopia is extreme (e. g., when there is loss of central fixation), total occlusion of the fixing eye is imperative. This can be

Various types of occluders. *A*, an elastoplast occluding pad; *B*, zinc adhesive tape fastened to the anterior surface of the lens; *C*, music-mending tape.

done only by means of (1) gauze pads held in place with adhesive isinglass tape, (2) pads held by a roller bandage or (3), most easily and effectively, by a prepared elastoplast (adhesive) occluding pad [11] (figure, *A*). I use one 2 by 3 inches in size and have the parent change it every second or third night unless it loosens sooner. Spectacle occluders or other types of occlusion attached to spectacles can be removed too easily by the patient and are not effective in the case of severe amblyopia. The small child (up to the age of 3 years) should return every seven to twenty-one days for an estimation of vision in each eye. I have seen 1 year old infants with no fixation in the right eye return after wearing an occlusion for two weeks with excellent fixation in the right eye and with no fixation in the left eye. The younger the patient, the more frequent the visits should be. Patients from the ages

11. These pads are manufactured under the name of "elastoplast coverlets" by Duke Laboratories, Inc., Stamford, Conn.

of 3 to 6 years may be seen not oftener than every six weeks, unless visits are necessary to boost the patient's morale and maintain interest. When the initial vision is less severely impaired, again the visits should be more frequent, since more rapid improvement may be expected.

As vision improves, foveal fixation becomes steady and the patient acquires an increased sense of security, the amblyopic eye should be stimulated by having the child do such things as tracing, drawing, cutting out paper dolls, threading beads, working puzzles and reading. The simple fact of occlusion may not stimulate the fovea as do these procedures, which require the effort to see better foveally.

Complete occlusion should be continued until vision of 20/70 or better is obtained. Then several methods of subtotal occlusion may be used. Plastic and rubber occluders which fit on the spectacle frame are

TABLE 6.—*Methods of Treatment of Amblyopia*

Occlusion
A. Total occlusion
Adhesive pad
B. Subtotal occlusion
(a) Spectacle occluders
(b) "Built-up" patch
(c) Music-mending tape
(d) Music-mending tape with atropine
C. Blurring
(a) Several (?) hours per day
(b) Alternate days or weeks
Stimulation of vision
(a) Tracing, reading, paper dolls, etc.
(b) Movies
(c) Flashing lights (?)
Morale boosters
(a) Rewards
(b) Penalties

useful. We have used chiefly two forms of subtotal occlusion. At times a large piece of zinc adhesive tape is fastened to the anterior face of the lens before the fixing eye, extending 1 inch (2.5 cm.) above the spectacle frame and well nasally, then being folded back on itself and fastened to the posterior surface of the lens. This gives effective occlusion of the lens, as well as above and nasally (figure, *B*).

More often the lens before the fixing eye is occluded by covering its posterior surface with music-mending tape (a translucent adhesive paper), through which light, but not form, may be seen (figure, *C*). This type of occlusion is not so obvious to the casual observer, and so it it not too unpleasant to the wearer. If the patient is inclined to peep over the spectacles, 1 drop of 0.5 per cent atropine sulfate should be instilled into the "occluded" eye daily. If any considerable degree of hypermetropia is then present, the blurred vision resulting from

atropinization discourages further attempts at peeping, and the patient is more inclined to use the nonoccluded (amblyopic) eye.

We have not used atropine alone for blurring, for several reasons. First, the hypermetropia must be considerable if atropine alone is to be effective. Second, the lack of occlusion makes the treatment of suppression and abnormal retinal correspondence less adequate. Third, light in the atropinized eye is annoying.

We have used clear nail polish, smeared or stippled on the lens before the fixing eye, as a finishing procedure. The patient who has 20/30 in one eye and 20/20 in the other will be encouraged by the presence of the substance to use the other eye but, at the same time, will have some opportunity for binocular vision. We have had much complaint of glaring of light through the polish, with subsequent confusion; so we use it infrequently.

As a finishing procedure, or to maintain vision in a previously amblyopic eye, we frequently use part time occlusion. In the patient who has vision of 20/20 — and a tendency to lose vision under orthoptic treatment, the vision may be maintained by use of music-mending tape for two to five hours in the evening while he is studying or reading. In this connection, it should be stated that the mere obtaining of good vision in the amblyopic eye offers no assurance that such vision will be maintained. Visual relapse is frequent, and during treatment the vision of each eye should be tested at frequent intervals.

A final comment on treatment of amblyopia should be made. The wearing of total occlusion by the small child, or of glasses occlusion by the older one, is not often accepted graciously. Rewards in the form of candy, extra movies or money must be offered. The "flat of the hand" must be used occasionally, but not if any other method will work. High praise must be heaped on the little patient if he wears his patch, and enthusiastic comment must be made about any small amount of visual improvement. The parents should understand that to the person with an amblyopic eye occlusion is the last court of appeal. The patient's false hopes that surgical intervention or "exercises" may cure the vision must be dispelled and the necessity of complete occlusion emphasized again and again. We feel that occlusion should be discontinued unless appreciable visual improvement can be shown after three months of conscientious effort. Treatment should be continued as long as improvement is evident. Often, the final vision is less than 20/20 even though the patient, the parents and the oculist have cooperated to the fullest. This is more likely to be true if the beginning of treatment was delayed or the initial vision poor. The best possible vision should be maintained until fusion and alinement have been gained, if possible.

EFFECT OF VISION ON SQUINT

Most of this study has been devoted to "how squint affects vision." We should like to comment on how vision affects the position of the eyes.

Chavasse [2] stated that an eye blind at birth and in early infancy will turn out, an eye blind in later infancy and in childhood will turn in, an eye blind in adolescence will turn in less, an eye blind in early adult life will be about straight and an eye blind in later adult life will turn out. We have analyzed 29 cases of squint in which there were organic ocular defects to determine the position of the eyes and the visual defect.

These cases of organic ocular defects (table 7) include 4 of congenital cataract, 2 of coloboma of the optic disk, 5 of congenital nystagmus, 6 of Duane's retraction syndrome, 8 of congenital myopia (4 of

TABLE 7.—*Vision and Organic Defects*

	No. of Patients	Ortho-tropia	Exo-tropia	Eso-tropia	Ambly-opia
Congenital cataract (or aphakia)	4	..	1	3	4
Coloboma of disk	2	..	1	1	1 (20/100 to 20/30)
Congenital nystagmus	5	..	..	5	3
Duane's (retraction) syndrome	6	3	1	2	1
Congenital myopia					
Monocular	4	..	2	2	3 (3/200 to 20/50)
Binocular	4	..	..	4	1
Congenital ptosis	1	..	1	..	0
Congenital glaucoma	3	..	2	1	?
Chorioretinitis	2	..	..	2	2

monocular and 4 of binocular type), 1 of congenital ptosis (pupil not covered), 3 of congenital glaucoma and 2 of chorioretinitis. Of this group of 31 cases there was definite amblyopia in 15, and the patients either were not candidates for treatment or did not respond to treatment. The vision of 3 patients could not be determined with any degree of accuracy.

Certain of this group had sufficient opportunity for foveal vision in each eye to insure that vision would not suffer. Of 6 patients with Duane's syndrome, the eyes of 3 were orthophoric in the primary position, though obviously misalined when abducting or adducting. Two had obvious esotropia, and 1 obvious exotropia, when the eyes were in the primary position. However, only 1 patient had amblyopia, for the other 5 had either spontaneous fusion or alternation.

Of 5 patients with congenital nystagmus (but with foveal fixation), 3 had amblyopia, and 2 of these were amblyopic in both eyes. There is some question whether mild foveal damage or the nystagmus was the

cause of the amblyopia. All 5 were esotropic and presented no opportunity for single binocular vision. Attempts at occlusion in cases of congenital nystagmus have been unsuccessful, largely because any type of covering of one eye causes a great exaggeration of the nystagmus, with accompanying confusion and annoyance. We feel that no treatment except the proper spectacles, or surgical intervention in cases of the severe squints, should be attempted.

One patient with congenital ptosis, with the lid margin just above the lower margin of the pupil, had no amblyopia because the opportunity for single vision was present part of the time. The squint was one of divergence excess.

Three patients with monocular congenital glaucoma seemingly have visual defects, but it cannot be determined whether this is due to the arrested glaucoma or to amblyopia ex anopsia or to both. Treatment with intermittent occlusion is being carried on. It is interesting that after the eye has been patched for two or three days these patients seem to become adjusted and are little inconvenienced in using the glaucomatous eye.

The 8 patients with congenital myopia fall into two groups. The 4 with bilateral myopia (with a myopia from 8 to 16 D.) were all esotropic, and only 1 was amblyopic. The 4 patients with monocular myopia had a high degree of myopia in one eye, and either slight myopia or moderate hypermetropia in the other eye. Two of these were exotropic and 2 were esotropic, and 3 of the group had extreme amblyopia in the myopic eye. One case is particularly interesting. A girl of 6 years was first seen with corrected vision of 3/200 in the right eye and 20/20 in the left eye. I did not encourage treatment, but the parents were insistent and the patient was cooperative. After nine months of continuous occlusion, vision in the right eye has improved to 20/50 + with a correcting lens of — 4.50 D. sph. ⊃ 4.00 D. cyl., axis 180. The parents understand that the probability of single binocular vision is slight, but a "spare" eye having 20/50 + vision may some day be important to this patient.

Four patients with congenital cataract all had at least one amblyopic eye, though treatment was begun early. We have found it most difficult to preserve two seeing eyes when one or both are cataractous and have to be treated surgically.

Two patients with chorioretinitis involving the general macular region had poor vision in the involved eye, and attempts at occlusion were entirely unsatisfactory.

Two cases of coloboma of the disk are included. The patient with the severer involvement did not respond to treatment and remained amblyopic. Vision of the patient with the less severe involvement improved from 20/100 (corrected) to 20/30 after five months of continu-

ous occlusion, and this improvement has been maintained with several short periods of part time occlusion. It is interesting that this patient has acquired third grade fusion and has largely overcome a divergence excess. Results in the 2 cases (1 of monocular myopia and 1 of coloboma of the disk) just cited, as well as in several similar ones not included in this series (not occurring in the portion of the file analyzed for this paper), have convinced us that in some cases of organic defect of the eyes there is a superimposed amblyopia ex anopsia. Treatment should be tried in all cases, for at least three months, unless the imposed handicap is extreme and persists.

ADDITIONAL COMMENT

Certain miscellaneous observations are worthy of comment. We have constantly noted that an amblyopic eye would seem to have poor abducting power, and we earlier assumed that the lateral rectus muscle was paretic. More recently, having cured much of the amblyopia, we have noted that abduction becomes normal as visual acuity improves.

Further, we have frequently noted that a squinter with an amblyopic eye has primary and secondary deviation. In other words, when the "good" eye is fixing, the deviation is less; but when the amblyopic eye is fixing, the deviation is greater. We have assumed that more accommodative effort is exerted when the amblyopic eye is fixing and that this causes a greater convergence.

These two points illustrate ways in which vision affects the function of muscles.

Our methods of analyzing our results of treatment of amblyopia are unsatisfactory and the figures obtained inconclusive. It is hoped that in a further, more complete, study the results may be published.

SUMMARY

1. A series of 407 cases of squint is presented.

2. A method of determining visual acuity by ability in foveal fixation is suggested.

3. The incidence of amblyopia is correlated with certain facts obtained from the history of patients with strabismus.

4. The incidence of amblyopia is correlated with certain ocular findings (e. g., type of squint, amount of squint and binocular refraction).

5. The treatment of amblyopia ex anopsia is discussed.

6. The relationship of organic ocular defects and amblyopia ex anopsia is discussed.

CONCLUSIONS

1. Visual acuity can be estimated in the infant by determining the ability in foveal fixation.

2. The greater frequency of amblyopia in patients with strabismus can be predicted from a history of "constant," or "monocular," deviation.

3. While the average age of onset of squint may not be significant, the average duration of the squint before treatment is most significant in the production of amblyopia.

4. "Visual confusion" occurs more frequently with exotropia and suggests a less severe degree of amblyopia.

5. Amblyopia is more frequent with convergent than with divergent squint, and with mechanical convergent than with accommodative convergent squint, and is least frequent with alternating squint and with "atypical" accommodative convergent squint.

6. The incidence of amblyopia increases directly with the degree of hypermetropia or the degree of anisometropia present.

7. Total occlusion is the treatment of choice for amblyopia ex anopsia and can be obtained only by "face patching."

8. Amblyopia ex anopsia may occur as the result of organic ocular defects and can be improved in some cases with treatment.

1605 Twenty-Second Street, N.W.

CONICAL CORNEA AND MONGOLISM

ANDREW RADOS, M.D.
NEWARK, N. J.

RECENTLY I had under observation 2 patients with bilateral conical cornea associated with mongolism, a man aged 22 and a woman aged 29; in the latter the conical cornea was complicated with cataract, commonly noted in older persons with mongolism. A perusal of the literature revealed as ocular symptoms of mongolism only nystagmus, convergent strabismus and blepharitis in some cases, in addition to the almost constant presence of the oblique palpebral fissure, with slanting of the lids up and temporalward and the epicanthus. A search of textbooks for mention of conical cornea associated with mongolism was futile; even such books as Tassman's,[1] when discussing ocular disturbances in conjunction with general systemic disease, failed to mention the occurrence of keratoconus. Conical cornea and mongolism are both anomalies, the nature of which is still a moot question.

Recognition of conical cornea is usually attributed to the observation of Taylor (1766); but Demours, in Paris, was actually the first (1747) to give an accurate description. Himly held the belief that the disease was a hyperkeratosis. The actual morphologic description was given by Wardrop (1819). R. Wagner's histologic examination revealed that the conical deformity depends on thinning of the central portion of the cornea, without the presence of inflammatory symptoms. In the majority of cases conical cornea is bilateral, to a variable degree; it affects female patients more often than male, and appears with and without rupture of Descemet's membrane. According to Stock, it is never congenital and appears usually after the age of 10 years; but experience has shown that often keratoconus is noted about the age of puberty, and there are rare instances of development at about the age of 40. The familial and hereditary tendencies suggest the possibility of a developmental disturbance, even though nothing is known of the nature of such a defect. Cases like Behr's,[2] in which conical cornea was associated with blue sclera and spontaneous luxation of various joints, are evidence in support of such an explanation, the develop-

1. Tassman, I. S.: The Eye Manifestations of Internal Diseases, St. Louis, C. V. Mosby Company, 1942.

2. Behr, C.: Beitrag zur Aetiologie des Keratokonus, Klin. Monatsbl. f. Augenh. **16**:281, 1913.

mental disturbance being more probable in cases in which conical cornea is associated with anomalies of various parts of the external membrane of the eye. In the cases in which a congenital anomaly apparently is not responsible, acquired changes representing dyscrasic factors were considered by many authors, including Elschnig, who hypothesized a chronic inflammatory disease of the endothelium and Descemet's layer.

In Geyer's [3] series of 30 cases of mongolism, 2 cases of bilateral conical cornea (in males 28 and 13 years of age, respectively, sibships 14 and 21) were mentioned; in my limited material 2 other cases were seen. Since persons with mongolism are short lived and conical cornea usually develops about the age of puberty, the occurrence of conical cornea in cases of mongolism should not be considered a rare coincidence. In order to determine the significance of simultaneous occurrence of conical cornea and mongolism, I shall review present knowledge concerning the two conditions.

MONGOLISM

CLINICAL CHARACTERISTICS

The first description of mongolism was given by Down [4] in 1886, the term mongolism being chosen because of the Kalmic, or Tartar, type of the features. Crookshank [5] tried to explain the condition as due to crossing with persons of the mongoloid race. The presence of mongolism in various races and the absence of the condition in crossings of Chinese and white persons or of Chinese and Negroes is ample evidence of the invalidity of such an explanation.

Children with this type of mental deficiency show a flat, broad face; oblique palpebral fissures; short nose with broad, depressed bridge; short, sparse, brownish black hair, and small, rounded head. The type of idiocy is considered to be due to antenatal arrest in development (both physical and mental), characterized by brachycephaly, combined in later years with the type of physiognomy seen in members of the mongolian races. The brachycephaly, or shortening of the antero-posterior diameter of the skull, is the most constant and distinguishing feature. Not only is the skull distinctly round, but the occipital region is flattened and the occipital protuberance is absent. The plane of the occiput tends to be parallel with the plane of the face and forehead; the anterior, posterior and transverse diameters of the skull are nearly

3. Geyer, H.: Zur Aetiologie der mongolischen Idiotie, Leipzig, G. Thieme, 1939.

4. Down, J. L.: Observations on Ethnic Classification of Idiots; Clinical Lectures and Reports, London Hosp. **3**:259, 1866.

5. Crookshank, F. G.: The Mongol in Our Midst: A Study of Man and His Three Faces, ed. 3, London, George Routledge & Sons, Ltd., and Kegan Paul, 1931.

equal, and the fronto-occipital circumference is greatly diminished. Of 26 patients, Geyer found 16 hyperbrachycephalic, 8 brachycephalic and 2 dolichocephalic. The fontanels and cranial sutures show delayed closure. The face is round, and often depressed, with chubby cheeks. At birth the children are undersized and extremely weak; growth is slow; later the child is well nourished and fat, especially near puberty. Puberty is reached late; the pubic and axillary hair is sparse. In the girl, menstruation occurs late, is irregular and ceases early. The eyebrows tend to run upward and slightly outward. The zygomatic bones are prominent; the palpebral fissures are narrow and slope down and in. Convergent strabismus or nystagmus, or both, most commonly the strabismus, is present. Epicanthus is a frequent, though by no means a constant, feature. There is hypotonia not only of the muscles of the extremities but of the muscles in general, hence, the typical facial expression and frequent slight ptosis (possibly due to hypofunction of the adrenal glands). The mouth is small, round and constantly open; the lips are somewhat everted, especially the lower one, which is usually thicker than normal. The tongue is protruding; the most striking feature appears some time after birth; the papillae become enlarged; the surface shows deep and numerous fissures (scrotal tongue). Deformities of the palate are common, the chief type being V shaped. Dentition is much delayed, and the teeth are frequently very irregular; the second dentition occurs at the proper age, and the teeth are less irregular. Congenital heart disease is commoner than with any other type of idiocy. Spinal curvatures do not belong to the picture and, if present, are only secondary to the general muscular weakness. Ossification is much delayed; the hands are short, broad and stumpy. The fingers are round and thick and taper toward the extremities; the thumb and the little finger are shorter in proportion to the other fingers than normal. Clinodactyly, camptodactyly or syndactyly is frequent. Laxity of the joints is a prominent feature, with a greater range of mobility than normal; this is due to laxity of the ligaments or, more probably, to deficient tonicity of the muscles. Undescended testes, hernia, deformity of the ears and separation of the great toe are often noted.

Defects of intelligence are early observed; walking and speech are delayed until the third year; the vocabulary is later very limited; failure to form sentences is characteristic. The child remains idiotic; death occurs usually in the first year, as a result of respiratory, intestinal or other infections; the older child with mongolism is susceptible to tuberculosis. Mental deficiency ranges from the mildest form of imbecility to complete idiocy. During infancy, the disposition is one of apathy ("good child, easy to manage"); later, the child is characteristically good tempered, cheerful, affectionate, playful and a lively mimic, with musical and dancing ability. Development of walking and movements is generally delayed.

ETIOLOGY OF MONGOLISM

Mongolism is characterized by generalized retardation of somatic, skeletal and mental development, in many instances resembling cretinism. Strange to say, the great Virchow was opposed to considering it a separate entity; he included it with the group to which congenital rachitis and sporadic cretinism belong. The former, congenital rachitis, is known as chondrodystrophia fetalis; similarly, myxedema and sporadic cretinism are entirely distinct from mongolism.

Evidence has been present that mongolism is associated with advanced maternal age. The development of mongolism has been said to be influenced by ill health in the mother, uterine exhaustion, increased amniotic pressure and defective nidation. In 56 per cent of Kreyenberg's [6] series of 50 cases the child with mongolism was the last born of the family; in 46.7 per cent the mother was 40 or older, and in about 50 per cent the mother was older than the father. Kreyenberg observed only 1 patient with mongolism in a family, but others have reported 2, 3 or even 4 such persons in the same sibship, an observation pointing to a certain functional depletion of the ovaries of the mother. The child with mongolism is often the last offspring of an older mother, but mongoloid children are born to young mothers as well—perhaps the first child, followed by normal, healthy children. According to Leeper,[7] 5 were first-born children; 90, last-born children, and 10 were the fifth or sixth in the sibship, followed by a premature infant or a stillbirth. Therefore, the correlation between maternal age and mongolism is not conclusive, and the theory of uterine exhaustion, postulated by Shuttleworth, does not explain the occurrence of children with mongolism who are born to young mothers. The possible role of defective nidation (development of endometrial epithelium in the intermenstrual period) was advocated by von der Scheer; accordingly, the local changes in the endometrium lead to poor developmental possibilities for the fertilized ovum. Extrauterine gestation, in which the placenta is attached in an unquestionably more undesirable location, producing, nevertheless, a living child free from mongolism, is against the possibility of this factor as a cause of mongolism. Space does not permit me to discuss other proposed, but less important, factors. Among these are alcohol; syphilis; previous frequent child bearing; toxic influences, leading to reproductive exhaustion; exhaustive illnesses during pregnancy; increased amniotic pressure; deficiency of vitamins and hormones during pregnancy (Tredgold),

6. Kreyenberg, G.: Der Mongolism, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 2.

7. Leeper, B.: Mongols, Rev. Neurol. & Psychiat. **10**:11, 1912.

leading to alteration of chromosomes; ovarian damage, preventing the maturation of the ovum (Geyer); diminished secretion of progesterone (Penrose [8]), resulting in disturbance in the embedding of the fertilized ovum; fetal hyperthyroidism (Clark), and possible damage from previous abortions (curettage and roentgen irradiation, Engler [9]), all of which have been suggested as having a direct influence on the development of mongolism. The evidence on which these assumptions were based is scanty and unconvincing. The hereditary influence, change in the germ plasm and disturbances in the glands of internal secretion are the most important factors investigated during the past decades and, consequently, are of sufficient significance to be considered here.

Endocrine Factors.—The possibility of an endocrine genesis of mongolism is often discussed, with particular reference to disturbances of the thyroid and the pituitary gland. In the majority of cases in the older literature pathologic changes in the glands were absent; nevertheless, Gordon [10] expressed the belief that at times a functional disturbance of the thyroid is present in mongolism, independent of the presence of demonstrable manifestations of hypothyroidism or athyreosis. Kassowitz' [11] expressed opinion was in agreement, that is, that persons with mongolism exhibit changes in the thyroid at times. Hill [12] reviewed the material from 20 autopsies on the thyroid gland in cases of mongolism. According to Wieland, the thyroid was observed to be normal on macroscopic and microscopic examination by most of the older authors; only a few noted the presence of hypoplasia and definite histologic changes and expressed the opinion that there was no evidence of the thyrogenesis of mongolism. Morphologic changes were described in 3 cases by Thomas and Delhougne.[13] An embryonic type of thyroid, with follicles and poor colloid content, was observed in a 3½ month old infant; the thyroid of a 21 month old child exhibited rich areas of colloid and others of embryonic type, with poor colloid substance; the thyroid of the third child, 8½ months of age, had abundant follicles but was still of undifferentiated tissue and poor colloid content. The authors considered the possibility that the changes were

8. Penrose, L. S.: Relative Aetiological Importance of Birth Order and Maternal Age in Mongolism, Proc. Roy. Soc., London, s.B, **115**:431, 1934.

9. Engler, M.: Causation of Mongolism, J. Neurol., Neurosurg. & Psychiat. **7**:27, 1944; Causation and Prognosis of Mongolian Idiocy, Proc. Roy. Soc. Med. **38**:211, 1945.

10. Gordon, M. B.: Morphological Changes in the Endocrine Glands in Mongolian Idiocy, Endocrinology **14**:1, 1930.

11. Kassowitz, M.: Infantiles Myxödem, Mongolismus und Mikromelie, Wien. med. Wchnschr. **52**:1049, 1105, 1202, 1256, 1301, 1357, 1409 and 1452, 1902.

12. Hill, B.: Mongolism and Its Pathology, Quart. J. Med. **2**:49, 1908.

13. Thomas, E., and Delhougne, E.: Schilddrüsenbefunde bei Mongolismus, Monatschr. f. Kinderh. **28**:519, 1924.

normal, as the embryonic stage may still persist at this age. Fromm [14] considered the development of the thyroid gland in his case as insufficient for the age of the patient (18 months); Brudzinsky [15] described the thyroid in his case as rudimentary, and Bernheim-Karrer,[16] as partially sclerosed and atrophied. Bourneville [17] observed involvement of the thyroid gland in 2 cases. In the first case, the trabeculae were hypertrophied; the vessels were sclerosed, and interstitial hemorrhages, slight pigment and fatty infiltration were noted, with slight, but pathologic, modification of the elements of the gland. In the second case, the thyroid showed alterations in all its elements. The colloid material in the vesicles was almost completely replaced with cells derived from glandular epithelium; the vesicles were choked with these cells, and some were filled with fat; there was extensive sclerosis of the glands, and the trabeculae were thickened and infiltrated with young connective tissue. Oberthür and Phillipe [18] described slight interstitial proliferation about the capillaries and small hemorrhagic areas with pigmentation of the connective tissue; Lange [19] noted the presence of colloid degeneration with interstitial proliferation. Numerous authors (Kaufmann,[20] Meltzer,[21] Comby,[22] Thiemich,[23] Chartier,[24] Tilloy,[25] Cozzolino [26] and Sutherland [27]) did not observe changes in the thyroid in cases of mongolism.

14. Fromm, J.: Sektionbefunde bei einem Fall von Mongolismus, Monatschr. f. Kinderh. **4**:245, 1905.

15. Brudzinsky, J.: Contribution à l'étude du myxœdéme infantile, du mongolisme et de la micromélie, Arch. de méd. d. enf. **11**:513, 1908.

16. Bernheim-Karrer: Ueber zwei atypische Myxödemfälle, Jahrb. f. Kinderh. **64**:26 and 746, 1906.

17. Bourneville: De l'idiotie mongolienne, Arch. de neurol. **16**:252, 1903.

18. Oberthür, J., and Phillipe, C.: Examen histologique de deux cerveaux d'idiots mongoliens, Compt. rend. de Bicêtre **3**:148, 1901-1902. Oberthür, C. R.: Progrès méd. **10**:44, 1904.

19. Lange, P.: Beitrage zur pathologischen Anatomie des Mongolismus, Monatschr. f. Kinderh. **5**:233, 1906.

20. Kaufmann, E.: Lehrbuch der spezielle pathologische Anatomie, Berlin, W. de Gruyter & Company, 1922, vol. 2, p. 410.

21. Meltzer: Mongolismus, Klin. Wchnschr. **57**:791, 1920.

22. Comby, J.: Le mongolisme, Arch. de méd. d. enf. **6**:746, 1903.

23. Thiemich: Sektionsbefund bei einem Falle von Mongolismus, Monatschr. f. Kinderh. **2**:134, 1903.

24. Chartier, M.: Mongolisme avec malformation cardiaque rare, Arch. de méd. d. enf. **9**:99, 1906.

25. Tilloy, G.: Contribution à l'étude du mongolisme, Bull. et mém. Soc. anat. de Paris **81**:473, 1906.

26. Cozzolino, O.: L'encefalo in un caso d'idozia mongoloide, Pediatría **29**: 49, 1921.

27. Sutherland, G. A.: Mongolian Imbecility in Infants, Practitioner **63**:632, 1899; Mongolian Imbecility in Infants, Lancet **1**:23, 1900; Imbecility of the Mongolian Type, Proc. Roy. Soc. Med. **2**:187, 1909.

Lange was the first to report pathologic changes in the adrenal glands—necrotic changes consisting in atrophy of the cell bodies and granular degeneration of the protoplasm. In Gordon's 2 cases there was pluriglandular involvement. In the first of his cases (age 14 months) there were cirrhosis and dysfunction of the thyroid, physiologic involution of the adrenal cortex with hypoplasia of the chromaffin substance and a normal pineal body except for the presence of a glia-lined cyst. In his second case (age 6 weeks) the thyroid and adrenal glands showed pathologic changes identical with those in the first case; furthermore, retrogressive changes, i. e., Hassall's bodies in increased numbers, hypoplasia of the cortex of the thymus and incipient atrophy of the anterior lobe of the pituitary body, were noted.

In spite of the paucity of pathologic changes, the possible endocrine origin of mongolism was considered by various authors. The fact that children with mongolism are the offspring of older mothers, and usually the last members of the series, when the procreative powers are at a low ebb, suggests disturbances in ovarian function, not only those based on the climacterium but those with broader pathologic implications.

The endocrinologic classification of these "ill finished" children is controversial. According to Werner,[28] a definite pathophysiologic factor must be instrumental in producing their distinguishing characteristics, which are so astonishingly similar, but which generally are not considered to constitute an endocrine entity. However, opinions have pointed to the endocrine glands, especially to the thyroid. Benda [29] is the strongest advocate of the role of endocrine pathology, maintaining that endocrine stigmas are not secondary to the defects of the central nervous system. According to him, mongolism, even if overlooked in some cases, is inevitably present at birth. The antenatal development must be independent of the endocrine glands of the embryo, as the associated malformations, such as syndactyly and septal defects of the heart, antedate the development of the endocrine glands of the embryo. Thus, the deficiency is due either to germinal inferiority or to agents within the maternal organism. Of the general characteristics of children with mongolism, Benda emphasized the features referable to the endocrine glands. The menarche is delayed; menstruation may cease entirely after a few years; there is immaturity in development of the sex organs, with absence of secondary sex characteristics. The tendency to obesity, retardation of growth, degeneration of the cartilage of the distal epiphyses and absence of premature ossification parallel the gonadal underdevelopment, dysfunction of the adrenal cortex or deficiency of the thyroid or pituitary gland, without fitting into any of

28. Werner, A. A.: Endocrinology, Philadelphia, Lea & Febiger, 1937.

29. Benda, J.: Endocrine Aspects of Monogolism, J. Clin. Endocrinol. **2**: 737, 1942.

the classic categories. Again, Benda stressed that if the age and sex of the patient with mongolism are considered, the apparent contradiction in the endocrine aspect disappears. The gonads of the babies with mongolism are normal; those of the adults show immaturity, with degenerative signs. Similarly, the cortex and medulla of the adrenal glands are normal after birth but fail to develop normally. The pathologic process is evident in the two outer layers; the zona fasciculata appears narrow, without the usual lipid contents. The thyroid was hypoplastic in all cases in his series, the seeming exception being 2 cases of lymphadenoid goiter and colloid goiter, respectively. Histologic examination after birth revealed large areas of microfollicular parenchyma without colloid or irregular fibrosis. After the age of 7 months the commonest general picture is that of hypoplastic colloid goiter. In contrast to the thyroid of cretinism, with its inability to produce and store colloid, the type associated with mongolism retains this ability but is inactive, owing to lack of stimulation by the thyrotropic hormone of the pituitary gland. The picture of the thyroid is that of a hypoplastic and hypofunctional gland. The pathologic changes in the gonads, according to Benda, are based on lack of gonadotropins from the pituitary gland and from those glands (adrenal cortex and thyroid) which influence the gonadal development. In a more recent work, Bixby and Benda [30] studied the production of androgens in persons with mongolism and established apparently normal levels, indicating the deficiency of androgens from the second source, the male gonad; this corresponds to the known pathologic facts, namely, that the male gonad tends not to reach maturity in persons with mongolism and that there is absence of spermatogenesis, due to lack of gonadotropic activity of the pituitary gland. On the other hand, in the female the urinary excretion of androgens was normal, especially considering the biologic immaturity, showing that the adrenal glands are not of primary pathognomonic significance.

Kreyenberg concluded that the disturbance of the entire system of internal secretion, including the vegetative centers, is either a primary polyglandular insufficiency or a secondary insufficiency, due to general developmental inhibition or to abnormal germ plasm. Portius [31] similarly reasoned that the disturbance of internal secretion, especially the great disturbance in development of the genital organs, is an important cause of mongolism. The case observed by Scheidt [32] is of questionable

30. Bixby, E. M. F., and Benda, C. E.: Androgens in Mongolian Idiocy, Am. J. Ment. Deficiency **49**:138, 1944.

31. Portius, W.: Mongolismus, Fortschr. d. Erbpath. **2**:281, 1938.

32. Scheidt, W.: Einige Ergebnisse biologischer Familienerhebungen, Arch. f. Rassen- u. Gesellsch.-Biol. **17**:129, 1925.

value, since the soft, toxic goiter, epicanthus, oblique palpebral fissure and yellowish skin gave the impression of mongolism, but the characteristics were only superficially similar and the picture was not that of true mongolism. Hill, in his first case, noted evidence of sclerosis of the thyroid, domination in number and size of the vesicles, though lined with regular cuboidal epithelium and filled with well staining colloid material, and greatly increased interstitial tissue with round cell infiltration; but he expressed the belief that there is as yet no evidence that any alteration, either in structure or in function, is responsible for this form of idiocy. It is generally accepted that infantile myxedema (cretinism), in which athyreosis probably exists in utero, is sharply differentiated from mongolism, the latter being characterized by absence of manifestations of hypothyroidism and the former showing striking improvement after administration of thyroid, particularly if the treatment is instituted early. Cameron [33] stated that the child with mongolism does not have hypothyroidism, although Benda asserted that the thyroid is hypoplastic, suggesting a resting colloid goiter, due to lack of stimulation of the pituitary body.

Hereditary Factors.—The endocrine background of mongolism is unconvincing, and the possible hereditary involvement has not escaped general attention. The correlation with maternal age and with familial occurrence are important factors, and the findings in twin research give valuable information.

The role of advanced maternal age in mongolism is obvious. According to Bleyer,[34] in 1924 the peak maternal age in this country was 24; the age of the mothers in a series of 2,822 mongoloid children was 41. Furthermore, the likelihood of producing a child with mongolism increases in direct proportion to the number of menstrual cycles through which the woman has passed. The important correlation with advanced maternal age is demonstrated by the fact that mothers from 15 to 19 years of age produced 3.4 per cent, or only one fourth of the expectancy as judged by their proportionate contribution to the total number of births, whereas the mothers from 33 to 39 years of age, producing only 0.9 per cent of births in the general population, gave birth to 23.8 per cent of the infants with mongolism, an excess over the expectancy of 25:1. The mothers in the succeeding age groups, of 40 to 44, showed a further increase above the expectancy of 75:1. Figures in various series are likely to show the existing correlation between mongolism and maternal age; the paternal age seems to be of no consequence.

33. Cameron, A. T.: Recent Advances in Endocrinology, ed. 5, Philadelphia, The Blakiston Company, 1945.

34. Bleyer, A.: Role of Advanced Maternal Age in Causing Mongolism, Am. J. Dis. Child. **55**:79 (Jan.) 1938.

Considering the familial occurrence, MacKaye [35] reported that less than 20 records are available in which mongolism occurred in more than one member of the family, and that in 1 case the patient had 4 similarly affected sisters. However, one must bear in mind that infants with mongolism are often born to mothers of advanced age and are the last in a series of children, and that the misfortune of having given birth to a child so distressing will often induce the parents not to have any more children, thus influencing the statistics of familial incidence. On the other hand, it is generally known that normal children have been born before and after a child with mongolism. The statistical figures could be interpreted as indicating that mongolism is not linked with any hereditable anomaly of the endometrium or any other inheritable affliction of the mother.

The question of hereditable or nonhereditable lesions of the germ plasm gave impetus to the research on twins with mongolism; its occurrence in twins contradicts the theory that an intrauterine lesion in the developing child is the etiologic factor. Concordance in identical twins and discordance in fraternal twins in the great majority of cases leads to the inevitable conclusion that the timing of the lesion must be placed before the moment of fertilization of the ovum. However, one must consider von Verschuer's opinion, namely, that the concordance of identical twins may be due to an early lesion of nonhereditary character or to a genuine hereditary change in the germ plasm, explaining the concordance of identical twins and the discordance of fraternal twins.

The literature contains 14 cases of monozygotic twins, all of whom were concordant; 58 cases of dizygotic twins (part of whom were of opposite sexes), with only 1 of the twins affected, and 4 cases of dizygotic twins (Russell [36]; MacKaye; Gordon and Roberts,[37] and Jervis [38]), with both twins affected (no twins of opposite sexes).

The research on twins with mongolism led Bleyer [39] to the conclusion that there is true gametic mutation of a degressive type. According to de Vries, in progressive mutation the new species possesses characteristics not present in the parents; in regressive mutation some factors are absent, though present in the parents, and in degressive mutation the offspring is essentially defective throughout its structure, lacking the power of further propagation—a gametic alteration, as

35. MacKaye, L.: Mongolism in Nonidentical Twins, Am. J. Dis. Child. **52:** 141 (July) 1936.

36. Russell, P. M. G.: Mongolism in Twins, Lancet **1**:802, 1933.

37. Gordon, R. G., and Roberts, F.: Paraplegia and Mongolism in Twins, Arch. Dis. Childhood **13**:79, 1938.

38. Jervis, G. O.: Mongolism in Twins, Am. J. Ment. Deficiency **47**:364, 1943.

39. Bleyer, A.: Indications That Mongolian Idiocy Is a Gametic Mutation of Degressive Type, Am. J. Dis. Child. **47**:342 (Feb.) 1934.

expressed in mongolism. MacKaye, noting that in the great majority of fraternal twins only 1 member was affected, rightly suggested the possibility of degressive mutation in the germ plasm, since regressive mutation would necessitate the occurrence of a rare mutation form in both ova, or possibly the fertilization of one ovum by two sperm cells in the case that both the fraternal twins had the disease, explanations considered as very unlikely by most geneticists. Jervis expressed the opinion that the possibility of mutation is not consistent with the occurrence of the disease in both of a pair of dizygotic twins; mutations being rare phenomena, the assumption that mutation took place independently in the two ova at the same time in 4 cases is highly improbable. Alteration of chromosomes (Macklin, Penrose) or, according to Waardenburg,[40] deficiency in chromosomes through failure to divide, chromosomal duplication or sectional deficiency, due to transposition or sectional duplication, was advanced as a germinal factor in mongolism. Chromosomal alterations are inherited dominantly or recessively, and this mode of inheritance is consistent with concordance in identical twins and with discordance in fraternal twins; it is also consistent with the possibility of concordance in a certain number of dizygotic twins. However, if in mongolism chromosomal factors operate exclusively, as Jervis asserted, the proportion of concordant and discordant dizygotic twins should be close to the proportion of sibships with 2 members affected to sipships with only 1 member affected. Although reliable data concerning this point are scanty, one may assume that no more, or probably less, than 1 per cent of the affected sibships show more than 1 member with mongolism. Furthermore, Jervis called attention to the fact that the proportion of concordant and discordant dizygotic twins is 68 per cent (seven times, or probably more), a significant discrepancy suggesting other than genetic factors. The assumption of defective ova would explain the concordance of identical twins but fails in the case of dizygotic twins; the role of defective nidation does not agree with the concordance of monozygotic twins; the incidence of discordance in monozygotic twins should be of the same order as that in dizygotic twins. Analysis of the findings in research on twins led Jervis finally to external factors as causative, thus explaining some concordance in monozygotic and in dizygotic twins but failing to explain the absence of discordance in monozygotic twins. Moreover, the numerical proportion of the groups, the complete concordance in identical twins and the extremely high percentage of discordance in fraternal twins, is inconsistent with such a hypothesis.

40. Waardenburg, P. J.: Das menschliche Auge und seine Erbanlagen, Bibliot. Genet. **7**:1, 1932.

The cause of mongolism is probably germinal, or is operative in the earliest embryonic period; but even the research on twins failed to give a decisive answer. The inconclusive evidence and the fact that mongolism is commoner among boys than girls led Rosanoff and Handy [41] to assume that, although the lesion of the ovum is essential, the spermatozoon is probably not without influence. The x-chromosome of the female-producing spermatozoon seems to have in some cases the power to protect the injured ovum against its tendency to develop into a child with mongolism. In this connection, the authors pointed to the observation that mongolism varies greatly in the severity of manifestations and generally exhibits the milder forms in girls, possibly owing to the partial protection by the additional x-chromosome of the female.

The ultimate cause of mongolism seems still to be undecided. The maternal age shows definite correlation; the aberration is established in the earliest prenatal life and probably is present in the ovum. Early environmental, perhaps ovarian, causative factors or inherent gene entities, rather than regressive mutational changes, are the chief agents. If the disease is inherited, the dominant type of inheritance is ruled out by the seriousness of the condition, which, eliminating the reproduction of the afflicted person, would lead to spontaneous eradication of mongolism itself. Therefore, the recessive mode of inheritance remains as the only possibility, but the characteristic criteria of this type are absent in the sibship of children with mongolism.

Of the ocular symptoms, the characteristic oblique palpebral fissure, the nystagmus, the bulging eyes and the blepharitis have already been mentioned. Concerning epicanthus, it should be stressed that the phenotypically identical anomaly is apparently genotypically different, as it shows dominant inheritance in the white race and in Japanese and Chinese crossings with members of the white race, but is recessive in Eskimos and in Hottentot crossings with white persons.

To the ophthalmologist, the occurrence of conical cornea and cataract formation in the older patients with mongolism is of great interest. The changes in the lens are not present in the very young patients with the disease; therefore, they are not congenital but develop later. The characteristic opacities in the lens are of the same type but of somewhat different distribution, like that in myotonia atrophica, and constitute only facultative, not obligatory, symptoms of mongolism. The first to report bilateral cataract in association with mongolism was de Sanctis.[42] Kassowitz and Suhsland each mentioned a case of stellate cataract. The

41. Rosanoff, A. J., and Handy, L. M.: Etiology of Mongolism, with Special Reference to Its Occurrence in Twins, Am. J. Dis. Child. **48**:764 (Oct,) 1934.

42. de Sanctis, G. E.: Osservazione sulla etiologica del cheratocono, Ann. di ottal. e clin. ocul. **65**:279, 1937.

first study of a large series, 19 of 28 cases of mongolism, was made by Pearce, Rankine and Ormond,[43] and the same cases were considered later, with good illustrations, by Leeper.[7] Cassel[44] mentioned 3 cases of cataract in 60 cases, and Geyer, 4 cases in 30 cases of mongolian imbecility; and the occurrence of such cataracts was confirmed by von der Scheer,[45] Jeremy, Koby, Weill and Nordman, Goulden, Pineles, Vontobel, Schroeder, Doxiades and Portius. Of the 60 patients who were reported on by von der Scheer, 10 were under the age of 10 years, with completely clear lenses; 14 were 17 years or older and all exhibited bilateral cataract, and the group between the two, comprising patients between the ages of 8 and 17 years, consisted of 32 persons, with 22 afflicted with cataract. The lenticular changes were not congenital and were characterized by slow progression, unlike that of tetany, which is always rapid. With age, the frequency and the intensity of cataractous changes show parallel increases. Pearce, Rankine and Ormond, similarly, could not detect lenticular opacities in children under the age of 9 years; the fully developed cataract was present only in the older patients, and the less mature form, in some of the other patients. The distribution of the opacities, according to Duke-Elder,[46] resembles closely that seen in cases of myotonia, although the arrangement of the opacities points to an earlier development.

The minute dots may be powdery or punctate; others are annular or flaky; some are of crystalline appearance. The majority are white, while others glitter with red or green light. The dots are located in the cortical portion, deep to the capsule, and are nearer the anterior than the posterior surface. They are best seen with focal illumination, the small size causing them to be invisible in transillumination. In the cases of mature cataract the opacities consist of two layers enclosing the clear fetal nucleus, the posterior lamella having its anterior face concave and corresponding in curve to the posterior surface of the lens. The anterior lamella is much flatter and is situated about midway between the center of the nucleus and the surface of the lens. The dots are more numerous axially than peripherally and never reach the equator. The posterior pole of the cataract coincides with the posterior pole of the lens and may be arranged in a stellar figure. The anterior pole of the cataract does not correspond with the anterior pole

43. Pearce, F.; Rankine, R., and Ormond, A.: Notes on Twenty-Eight Cases of Mongolian Imbeciles, Brit. M. J. **2**:187, 1910.

44. Cassel: Ueber Missbildungen am Herzen und an den Augen bei Mongolismus der Kinder, Berl. klin. Wchnschr. **44**:159, 1917.

45. von der Scheer, W.: Cataracta lentis bei mongoloider Idiotie, Klin. Monatsbl. f. Augenh. **62**:155, 1919.

46. Duke-Elder, S. W.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.

of the lens. Leeper mentioned that the fully developed form may be described as lamellar cataract and the slighter form as congenital punctate cataract. The descriptions of later observers agree with that outlined here; some investigators, such as Vontobel, designated it as cataracta cerulea of the deeper cortical layers, and von der Scheer noted perinuclear cataract in 2 of his 80 cases. Fleischer attributed the formation of cataract in cases of myotonia to disturbance of the glands of internal secretion, and Duke-Elder pointed to the hypofunction of the thyroid in cases of mongolism as a possible basis of the lenticular opacities.

The inner eye shows the lenticular changes in large proportion of the older patients with mongolism, but, less frequently, central and paracentral degenerative patches of the retina and macular degeneration were also noted in the older group. An exception is the case of Boros,[47] in which a 5 month old infant with mongolism had a small, pigment-framed hole in the right macula and a large, disk-sized, oval, pigment-framed, sharply punched-out hole in the left macula. In this case the hole formation was due to intrauterine degeneration, as indicated by the ring of pigment surrounding the hole; nevertheless, the absence of retinal development could not be excluded.

CONICAL CORNEA

ASSOCIATION WITH VERNAL CONJUNCTIVITIS

In the introductory section, the occurrence of conical cornea with mongolism was mentioned, the only generalized systemic disease known to be associated wtih the development of this corneal lesion. Of the local diseases of the eye, vernal conjunctivitis is known to be associated with conical cornea, as first described by Lodato, in 1910, and confirmed by Tristiano, Rizzo, Gennaro,[48] Padovani,[49] Bietti [50] and Satanowsky.[51] The relation of vernal conjunctivitis and keratoconus was based on the opinion expressed by the authors that the endocrine disturbance was responsible for the two conditions; Parovani's patient, a man aged 22, had vagotonia (dermographia, the oculocardiac reflex and a strong reaction to vagotropic substances) and showed a feminine distribution of

47. Boros, B.: Beiderseitige Lochbildung in der Macula lutea bei mongoloider Idiotie, Klin. Monatsbl. f. Augenh. **103**:91, 1939.

48. Gennaro, G.: Sui singolari rapporti tra il cheratocono e il catarro primaverile della conjunctiva, Gior. med. mil. **76**:464, 1928.

49. Padovani, S.: Aritmia endocrina in soggetto primaverile con cheratocono, Lettura oftal. **2**:442, 1934; abstracted, Zentralbl. f. d. ges. Ophth. **33**:213, 1935.

50. Bietti, G.: Sui risultati del metodo interferometrico nel campo endocrinologico oculare, Boll. d'ocul. **17**:370, 1938.

51. Satanowsky, P.: Vernalis and Conical Cornea, Acta Cong. argent. oftal. **2**:193, 1938.

hair and fat and acrocyanosis. Bietti, by using the interferometric method of Hirsch, concluded that dysfunction of the genital organs was the plausible explanation in his 2 cases.

ENDOCRINE AND HEREDITARY FACTORS

In the vast majority of cases of conical cornea the lesion occurs in apparently healthy persons; disregarding the cases associated with mongolism and vernal conjunctivitis, one may consider the etiologic theories as of two types: The first type endeavored to explain conical cornea as a partial symptom of disturbance of the glands of internal secretion; the second looked to inheritance to furnish the unknown cause of the development.

The possible involvement of the endocrine system in cases of conical cornea became a much discussed problem after Siegrist [52] pointed to hypothyroidism as an important factor. Endocrine imbalance may influence the cornea, a primarily supportive tissue, a claim borne out by the bilateral appearance of conical cornea, often at about the age of puberty. Thus, conical cornea was regarded as an environmental anomaly in the older literature, at a time when blood pictures due to such conditions as chlorosis, anemia, undernourishment and underweight were unknown. Dor reported a case of bilateral conical cornea with exophthalmic goiter in which organotherapy effected improvement in both conditions; however, it is hard to believe that any treatment would result in *restitutio ad integrum*, the complete disappearance of clinical changes, once established, and the reappearance of a normal cornea in man. The results of animal experimentation cannot be applied directly to the explanation of conical cornea in human beings; it is more than questionable whether the condition produced in animals is identical in development. The experimental results of Mutch and Richards,[53] postulating that conical cornea is a vitamin A deficiency disease, must be regarded cautiously. Gudjonsson was the first to mention that in his experiments, in which keratomalacia was produced by a vitamin A–free diet, conical cornea developed frequently; but Mutch and Richards stated that the illustrations presented not keratoconus but buphthalmos. The latter authors administered a vitamin A–free diet to rats after weaning until the appearance of clinical symptoms of the deficiency were noted, and subsequent administration of large doses of vitamin A produced an acute form of conical cornea; if the vitamin was given early, the eyes cleared up completely and rapidly. The conical cornea was

52. Siegrist, A.: Die Behandlung des Keratoconus, Klin. Monatsbl. f. Augenh. **56**:400, 1916; Zur Aetiologie des Keratokonous, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **38**:187, 1912.

53. Mutch, J. R., and Richards, M.B.: Keratoconus Experimentally Produced by Vitamin A Deficiency, Brit. J. Ophth. **23**:381, 1939.

reversible in their experiments, and the cornea regained its normal contours, with only nebulas persisting. In the majority of their cases anterior synechias were noted; the pupils either failed to dilate or dilated only irregularly, changes which led the authors to suggest that increased intraocular pressure may have been the causative factor. Interesting as these experiments are from the standpoint of vitamin A deficiency, one must note, first, that the picture was reversible and complicated by intraocular changes; second, that, as shown in the illustration, the process not only involved the central portions but extended in all directions to the periphery, features hardly like those of conical cornea in man.

Siegrist noted that conical cornea occurs in delicate, nervous, pale persons, with dry skin, decreased perspiration, loss of hair and poor memory; and examination of the blood by Siegrist and Kottman revealed increase of lymphocytes and accelerated coagulation time, suggesting hypothyroidism. Strebel and Steiger[54] established that patients with known hypothyroidism, e. g., myxedema, do not have conical cornea, and they could not confirm the findings of Siegrist and Kottman. Of 9 patients with hypothyroidism, 6 did not show these changes; 3 had a slight increase of lymphocytes, and all 9 had normal coagulation time; the clinical symptoms were either absent or present to such a minimal degree as that encountered in normal persons without involvement of the thyroid gland. Siegrist countered with criticism of Strebel and Steiger's case histories, asserting lack of clarity and claiming that a patient may exhibit typical features in the beginning or during the period of progression, but that the absence of these signs after the condition has persisted for twelve to sixteen years is not conclusive. Furthermore, the reliability of the lymphocyte count was questioned by Siegrist, since Strebel and Steiger did not make the tests when the stomach was empty, and the digestive leukocytosis might interfere with the picture of an increased lymphocyte count. Siegrist observed conical cornea in 2 persons each 17 years of age, 1 with endemic cretinism and atrophy of the thyroid gland and the other a mongolian idiot. The case of Scheidt (not one of mongolism) and Wibo's case of conical cornea accompanying myxedema are further examples of conical cornea with an established pathologic condition of the thyroid. Nevertheless, these observations are meager as compared with the extensive distribution of thyroid disturbances in the population in general.

Von Hippel,[55] following the reasoning of Siegrist, expressed dissatisfaction with the view of the significance of the clinical symptoms

54. Strebel, J., and Steiger, O.: Ueber Keratokonus: Seine Beziehungen zur inneren Sekretion und zum intraokularen Druck, Klin. Monatsbl. f. Augenh. **15**: 260, 1913.

55. von Hippel, E.: Zur Aetiologie der Keratokonus (Untersuchungen mit der Abderhaldenschen Dialysierverfahren), Klin. Monatsbl. f. Augenh. **16**:273, 1913.

of endocrine disturbance in cases of conical cornea, since they are inconstant and do not permit any conclusion as to which gland is at fault. To bring further clarity to the problem, he employed the method, at that time considered more dependable, the dialyzation test of Abderhalden. In 2 typical cases and in 1 closely related case, the serum reacted to thymus—in 1 exclusively and in the others more strongly than to any other gland employed. Next to the thymus, a strong reaction was obtained to the adrenal gland in 2 cases; the reaction to thyroid was negative in 1 case and slightly positive in 2 other cases. In 1 case there was a slight reaction to pancreas; in another, a questionable reaction to the pituitary gland. In a later series of cases,[56] the reaction in 1 case was positive to thymus and testis and only slightly positive to thyroid; in a second case, slightly positive to thymus and thyroid; in a third case, slightly positive to thyroid, thymus and pancreas, and in a fourth case, positive to thymus, thyroid and spleen. On the basis of these results, he concluded that a relation between conical cornea and disturbance of the endocrine glands probably exists, but he warned of difficulty in interpretation, as the behavior of serums differs with time, a formerly positive reaction becoming negative and thus complicating the question, especially in cases of long standing. Hack[57] applied the same method in 3 of his cases; in the first case, a positive reaction was registered to brain and exophthalmic goiter tissue (negative in a subsequent examination five weeks later); in the second case, one of keratectasia following syphilitic keratitis, the reactions were negative, and in the third case the reaction was positive only to thymus. Dodge,[58] in 4 of 5 cases, observed an increased urinary excretion of sugar in the glucose tolerance test; this increase, due to a low normal threshold, suggests a lesion of the pituitary gland or the floor of the third ventricle. In a second series, of 34 cases, von Hippel[59] reported negative reactions in 6 cases, multiple reactions in 20 cases, with a reaction to thyroid only in 1 case and to thymus only in 7 cases, the total number of positive reactions to thyroid being 17 and to thymus 25. The series proved the occurrence of multiple reactions to various glands. These results were misunderstood by Kraupa,[60] who interpreted them as inconsistent, thinking that Siegrist suggested hypothyroidism as a

56. von Hippel, E.: Ueber die Behandlung des Keratokonus mit den Muellerschen Kontaktgläsern, Klin. Monatsbl. f. Augenh. **60**:49, 1918.

57. Hack, J.: Zur Aetiologie des Keratokonus, Arch. f. Augenh. **76**:259, 1915.

58. Dodge, W. M.: Keratoconus: Report of Five Cases, Am. J. Ophth. **21**: 40, 1938.

59. von Hippel, E.: Untersuchungen über Keratokonus mit dem Abderhaldenschen Dialysierverfahren, Arch. f. Ophth. **90**:173, 1915.

60. Kraupa: Physiognomisches bei Keratokonuskranken, Ber. d. deutsch. ophth. Gesellsch. **43**:294, 1922.

factor in the causation of acquired conical cornea, followed by dysfunction of the thymus and ovaries, and questioned why, for example, the parathyroid glands and the pancreas, glands which clinically are known not to result in the formation of conical cornea, were not similarly mentioned. Kraupa's argument was fallacious; a pluriglandular involvement remains an unproved possibility, as von Hippel's results can be interpreted only as a pluriglandular reaction, with predominance of the thyroid and thymus. The results of Schnaudigel [61] are further proof in support of this hypothesis. Of 9 cases, a positive reaction to thymus was registered in all, to thyroid in 5 and to the pituitary gland in 4 (only 6 cases were studied). Lymphocytosis was noted only in 2 cases, of the severe form. According to Schnaudigel, the positive reaction to thymus occurs so often in cases of toxic goiter and status thymicolymphaticus that its significance must be denied.

The endocrine involvement has often been questioned on account of undoubted unilateral disturbances; but this argument is not convincing, as proved by the occurrence of unilateral exophthalmos in cases of toxic goiter. The frequent development of conical cornea with the menarche, its relatively infrequent appearance at the menopause and the progressive course during the latter in cases of long standing (Killick) are suggestive of gonadal disturbance, possibly due to dysfunction of the pituitary gland. In 1 of Siegrist's cases, von Hippel found a positive reaction to ovary, and gynecologic examination disclosed infantilism; a similar case was observed by von Hippel, in which a 19 year old girl appeared to be only 14. Imré reported 4 cases with dysfunction or hypofunction of the ovaries; Padovani, a case of acrocyanosis and feminine distribution of the pubic hair and fat, and Meerhoff, Meerhoff and Montes Pareja,[62] the case of a 14 year old boy with genital hypoplasia and symptoms of dystrophia adiposogenitalis without any change in the sella turcica. In Gennaro's cases of 2 brothers, aged 19 and 26, respectively, the genitalia were poorly developed, and Jaensch's [63] patient, a boy aged 14 years, had dystrophia adiposogenitalis.

Dysthyroidism may serve as explanation of conical cornea in the case of Augstein,[64] in which toxic goiter was accompanied with dry,

61. Schnaudigel, O.: Zur Therapie des Keratokonus, Klin. Monatsbl. f. Augenh. **69**:466, 1922.

62. Meerhoff, W.; Meerhoff, A., and Montes Pareja, J.: Arch. de oftal. de Buenos Aires **4**:129, 1929.

63. Jaensch, P. A.: Keratokonus, Med. Klin. **25**:862, 1929; Keratokonus, die Ergebnisse der Forschungen der letzten 20 Jahre, Zentralbl. f. d. ges. Ophth. **21**: 305, 1929.

64. Augstein, C.: Zur Aetiologie und Therapie des Keratokonus, Klin. Monatsbl. f. Augenh. **51**:417, 1913.

pale skin, dystrophia of the nails and lymphocytosis, but no change in the coagulation time. Similarly, Verderame [65] observed parenchymatous enlargement of the thyroid, especially on the side of the large conical cornea. Sitchevska reported hypothyroidism in 6 cases; the trophic disturbance manifested itself in falling of the hair, brittleness of the nails, dryness of the skin (4 cases), hypertrichosis (1 case), increase of lymphocytes (3 cases), acceleration of coagulation time (4 cases) and a normal basal metabolic rate in all cases. The Abderhalden test disclosed hypofunction of the thyroid and thymus in 1 case; the blood calcium in all cases was within normal limits, and no rarefaction of the cranial bones was noted. Of Natale's 3 cases, negative reactions to thyroid were established in 2 cases, and positive reactions to thymus (with ovary, testis and pituitary), in 3 cases. Amoretti noted more positive reactions to thyroid than to thymus; Hack had a positive reaction to thymus in 1 of 3 cases. Suzuki,[66] with the interferometric method, reported dysfunction of the thyroid and pituitary gland in 1 case. In 3 of de Sanctis' 5 cases (1 of mongolism), the sella turcica was enlarged sagittally without clinical signs of endocrine imbalance, but possibly abnormalities of the pituitary gland were responsible for the enlargement of the sella. Velhagen [67] described an acute form of conical cornea with trophic disturbances and with questionable involvement of the thyroid and parathyroid glands. Dysthyroidism was claimed as the etiologic factor in 2 cases by Tamasheff [68]; tachycardia was present in both cases, and lymphocytosis and accelerated coagulation time were noted in 1. In 1 of Fleischer's [69] cases the Abderhalden reaction to thymus was positive, but it is noteworthy that, in Kraupa's opinion, the case represented keratectasia rather than conical cornea. In 11 cases reported by Fleischer and associates,[70] neither lymphocytosis nor acceleration of the coagulation time was evident; anomalies of the thyroid were associated with only 2 of his cases, in the form of slight enlargement but without anomalies of the hair, nails or skin. Groth, Hack and Uhthoff,[71] similarly, denied the endocrine basis of

65. Verderame, F.: Weitere Beiträge zum Verhalten der Pupille beim Keratokonus, Klin. Monatsbl. f. Augenh. **78**:145, 1927.

66. Suzuki, S.: Acta Soc. ophth. jap. **35**:1336, 1931.

67. Velhagen, K.: Einzelbeobachtungen über Störungen der inneren Sekretion und Auge, Klin. Monatsbl. f. Augenh. **96**:577, 1936.

68. Tamasheff, I. I.: The Etiology of Keratoconus, Russk. vrach **13**:127, 1914.

69. Fleischer, B.: Beitrag zur Klinik des Keratokonus, Arch. f. Augenh. **74**: 110, 1913.

70. Fleischer, B.; Schloessman, and Broesamlen: Beitrag zur Klinik des Keratoconus, Arch f. Augenh. **74**:110, 1913.

71. Uhthoff, W.: Weitere klinische und anatomische Beiträge zum Keratokonus, Klin. Monatsbl. f. Augenh. **56**:385, 1916.

conical cornea; Uhthoff found slight tachycardia with leukocytosis in 1 instance and slight toxic goiter with tachycardia in 2 others; in his opinion, the presence of minimal general disturbances does not warrant the assumption of any link between the endocrine status and conical cornea.

Imre [72] and von Szily [73] independently cited Török and Redway's [74] 3 cases, in which there were a decreased basal metabolic rate, anemia, signs of disturbance of calcium metabolism and changes in the cranial bones, but both fortuitously omitted to mention Török's second paper,[75] contradicting his own previous findings. The researches of Blackberg and Knapp [76] belong in the same category. They reported consistent production of conical cornea in dogs and rats fed a diet deficient in vitamin D and low in calcium, pointing out the importance of calcium-phosphorus metabolism in the development of the cornea.

An entirely different approach to the problem of conical cornea was presented by Vázquez and Barriére. They observed a greater than normal prominence of corneal nerve filaments and diminution of corneal sensibility in cases of venereal lymphogranuloma and obtained a positive reaction to the Frei test in all of a series of 14 cases of conical cornea. May confirmed the results by obtaining a positive reaction in all but 1 of his 29 cases. Nevertheless, Rocha [77] arrived at contradictory results. Of 20 patients, only 3 had a positive reaction to 0.1 cc. of the Frei antigen, and 6 who reacted negatively were retested with 0.3 cc., with a positive reaction in only 1 case. On the other hand, examination for an endocrine factor in 10 cases revealed hypothyroidism in 7 cases, hyperthyroidism in 2 cases and hypogonadism in 1 case.

Von Hippel maintained that Siegrist's opinion concerning hypothyroidism as an etiologic factor was well founded but called attention to the involvement of the thymus, as shown by serologic tests. The symptoms of disturbance of the thymus are much harder to detect than the distinct clinical symptoms of imbalance of other glands, such as the

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72. Imre, J.: Eye Diseases and Symptoms Connected with the Gonads, Adrenals, and Pregnancy, Tr. Internat. Ophth. Cong. (1937) **3**:181, 1938.

73. von Szily, A.; Schildrüse und Auge, Tr. Internat. Ophth. Cong. (1937) **3**:103, 1938.

74. Török, E., and Redway, L. D.: A Preliminary Report of Three Cases of Keratokonus, Arch. Ophth. **57**:19, 1928.

75. Török, E.: Three Cases of Keratoconus: Final Report, Arch. Ophth. **4**: 348 (Sept.) 1930.

76. Blackberg, S. N., and Knapp, A. A.: Ocular Changes Accompanying Disturbances of Calcium-Phosphorus Metabolism, Arch. Ophth. **11**:665 (April) 1934. Knapp, A. A.: Vitamin D Complex in Keratoconus: Etiology, Pathology and Treatment of Conical Cornea, J. A. M. A. **110**:1993 (June) 1938; Results of Vitamin D Complex Treatment of Keratoconus, Am. J. Ophth. **32**:289, 1939.

77. Rocha, A.: Keratoconus, Rev. brasil. oftal. **3**:123, 1945.

thyroid or the gonads. Various observers have advanced the hypothesis that one of several glands or a polyglandular involvement is the causative factor. Duke-Elder mentioned a possible endocrine involvement but, at the same time, emphasized the hereditary aspect of the problem.

The familial occurrence of conical cornea, or horizontal inheritance, was noted as early as 1828 by von Ammon in 3 members of the same family, and Horner described the vertical inheritance of the defect in two generations. Since these observations, there have been numerous references in the literature to the familial and hereditary occurrence of keratoconus. Various authors have observed the anomaly within the same sibship: Stähli [78] described it in 2 sisters; Wölfflin, in 2 sisters (according to the history, the father and mother were also affected [Wolz's [79] third case]); Killik, in 2 families; Haab, in 2 brothers (the lesion was more pronounced on the right side); Borel, in 2 brothers (Wolz's second and fourth cases); Gennaro, in 2 brothers; van der Hoeve,[80] in a brother and sister, and in a brother and 2 sisters; Weill,[81] in a brother and sister in 2 families; Dor, in several members of the same family (always on the left side); Kaelin-Sulzer,[82] in 2 brothers in a family of 8 children (consanguinity was not proved, but it could not be entirely excluded, for the parents had the same family name and so the relation of the mother's parents may have gone back farther than could be ascertained); Rumpf,[83] in 2 sisters (with brittleness of the nails), in a sister and 2 brothers and in a brother and sister (consanguinity was not present); Abelsdorff,[84] in 2 sisters, and Sander,[85] in 3 sisters, whose father had keratoconus. All the 4 affected persons in Sander's observation had various degrees of long-standing and neglected trachoma with sequelae, vascularization and scars of the cornea and entropion; all 4 members had anterior polar cataract with the conical cornea (similar to the observation of de Lapersonne).

Cases showing vertical inheritance are those of Clausen (mother and daughter), Haab, Wachter, Weill and Coppez (father and son) and the

78. Stähli, J.: Weitere Mitteilungen über die Vererbung des Keratokonus, Klin. Monatsbl. f. Augenh. **75**:465, 1925.

79. Wolz, O.: Zur Frage der Vererbbarkeit des Keratoconus, Arch. f. Augenh. **92**:156, 1923.

80. van der Hoeve, J.: Vererbbarkeit des Keratokonus, Ztschr. f. Augenh. **52**: 321, 1924; **53**:342, 1924.

81. Weill, G.: Sur l'etiologie de kératocône, Ann. ocul. **164**:668, 1927.

82. Kaelin-Sulzer, M.: Zwei Brüder mit Keratokonus, Klin. Monatsbl. f. Augenh. **103**:513, 1939.

83. Rumpf, J.: Contribution à l'étude de l'hérédite du kératocône, Inaug. Dissert., Lausanne, 1937.

84. Abelsdorff, G.: Ein Beitrag zur Erblichkeit des Keratoconus, Arch. f. Augenh. **103**:293, 1930.

85. Sander, P.: A Family Affected with Keratoconus and Anterior Polar Cataract, Brit. J. Ophth. **15**:23, 1931.

previously mentioned case of Sander (father and 3 daughters). All these cases were instances of hereditary transmission within two generations, but transmission through three generations was described by de Lapersonne and Stähli. In the family observed by de Lapersonne, conical cornea and congenital cataract occurred either singly or in associated form. Stähli found 5 affected members among 9 persons comprising three generations. A normal female and an afflicted male member constituted the first generation. The only son of the affected male was similarly affected; the unaffected female had 5 children (4 girls and 1 boy), the second and fourth daughters being affected. The third daughter of the sibship, herself unaffected, had an affected daughter. There was no consanguinity. In two generations the unaffected females, and in one generation the affected male, were the transmitters. The pedigree in Abelsdorff's case shows 2 brothers in the first generation, 1 of whom was affected and 1 unaffected; the former had 7 daughters and 7 sons, and 2 daughters were afflicted in the second generation, the transmitter himself being unaffected.

Conical cornea affected cousins in the cases of Borel and von Mandach (Wolz's fifth and sixth cases), Abelsdorff (the mothers and fathers were brothers and sisters) and Vogt [86] (the older patient was the niece of the father of the younger one).

Hereditary transmission has been claimed in certain cases of conical cornea by various authors; but opinions as to the mode of inheritance is not unanimous, and therefore the type of hereditary involvement is uncertain. The congenital forms were occasionally associated with intrauterine or early developmental anomalies, such as blue sclera (Behr), microcornea, persistent pupillary membrane, anterior polar cataract (de Lapersonne, Sander), pigmentary degeneration of the retina, medullated nerve fibers, atrophy of the optic nerve and inflammatory changes in the optic nerve and sheath (Salzmann). According to Franceschetti,[87] the uncomplicated form of hereditary conical cornea often seems to follow the recessive mode of inheritance, being often observed in the same sibship and coupled with consanguinity in some instances; on the other hand, its appearance in successive generations would testify against the recessiveness; possibly, therefore, its mode of inheritance is either dominant or irregularly dominant. Ida Mann expressed the belief that the inheritance is recessive or irregularly dominant and called attention to the unilateral appearance in all members of the same family. With regard to the latter statement, one must

86. Vogt, A.: Neue histologische Befunde bei Cornea guttata, Ztschr. f. Augenh. **84**:21, 1934.

87. Franceschetti, A.: Vererbung von Augenleiden, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1931, vol. 1, p. 732.

recall that the expression of a hereditary factor may differ greatly, as shown by polydactyly, which is a typical instance of simple dominant inheritance. The bilateral expression may be greatly modified as a result of variations in expression of the gene, due to differences in respect to other genes or differences in environmental conditions or both, or to the presence of inhibiting or modifying genes, producing only unilateral expression of the gene. However, in cases of conical cornea one would have to observe the family for a long time, for the manifestly normal eye may develop conical cornea after an interval of many years, or the conical cornea of the other eye may be represented by *forme frustre*, with a high degree of astigmatism, without the clinical picture of keratoconus. The occurrence of hereditary unilateral conical cornea seems not to be outside the realm of possibility; but the available data are insufficient for a conclusion, and it remains for future research to establish its occurrence with certainty. Schieck [88] accepted the hypothesis of the hereditary disposition of the condition but pointed out that, nevertheless, cases of congenital conical cornea had not been observed. This apparent contradiction is refuted by knowledge that conical cornea belongs in the group of conditions of homochronous inheritance, with the usual manifestation about the age of puberty. Waardenburg gave the mode of inheritance as recessive or dominant. However, the pedigree in van der Hoeve's case is typical of recessive transmission, as proved by the numerical ratio of the homozygotes and heterozygotes. Similarly, Clausen claimed transmission as a recessive, but suggested the possibility that conical cornea is not a simple factor and that its heredity may therefore be complex.

CONICAL CORNEA AND MONGOLISM

The available data on mongolism and conical cornea are sufficient to be conclusive. The association of the two conditions was at first only occasionally mentioned by de Sanctis and Siegrist, but the accumulation of cases demonstrate that the occurrence is not due alone to chance but belongs, like the cataract of older persons with mongolism, to the facultative characteristics of mongolian imbecility. The occurrence must, of necessity, be infrequent; conical cornea is rare in young persons (Gilbert noted it in 2 patients, 7 and 8 years of age, respectively). In Jaensch's compilation of 56 cases (20 male and 36 female patients) the congenital type occurred in 2 cases; the lesion developed between the ages of 10 and 14 in 8 cases, between the ages of 15 and 24 in 31 cases, between the ages of 25 and 29 in 7 cases, between the ages of 30 and 39 in 1 case and after the age of 40 in 1 case. In the majority

88. Schieck, F., in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1931, vol. 4.

of cases conical cornea develops at about the age of puberty or shortly after; on the other hand, the majority of children with mongolism do not reach the age of puberty, these two facts explaining the relative infrequency of the combination.

The mechanism of the establishment of conical cornea must be based on differences in degrees of consistency either of the entire cornea or of the central portion, whether the concept of a developmental anomaly or a disturbance of growth is accepted. The decrease in consistency due to structural deficiency of the tissues, mainly of the elastic elements, was suggested by Parisotti; decrease in the elastic coefficient, suggested by Parinaud and Pollak, and congenital weakness of the corneal center (or degeneration of Descemet's membrane), proposed by Ellis,[89] were unsatisfactory in themselves to explain even the congenital cases, and therefore additional local factors, such as increased intraocular pressure or inflammatory changes in Descemet's membrane or the endothelial layer, were sought, but were proved not to be operative. Additional causes of the mechanism were sought, such as an acquired decrease in resistance due to disturbances in the glands of internal secretion—mesenchymal weakness due to deficiency of the pituitary gland, or hypofunction of the gonads, thyroid or thymus—avitaminosis or calcium deficiency. The question of decreased resistance as a factor in conical cornea remains unanswered; Stähli[90] turned to the biologic law of variability in keratoconus. The curvature and measurement of the cornea are elements in the variability; Stähli assumed that this variability is operative in determining the thickness of the cornea, resulting in the two extremes, the very thick and the very thin type, the latter being necessarily of decreased resistance; the same variability must govern the elasticity and resistance coefficients. This variability, in accordance with biologic laws, can be postulated only, for there are no means of clinical measurement, and histologic examinations are entirely unreliable, owing to the presence of various late changes.

The question of variability leads to the hereditary involvement of the germ plasm, for hereditary weakness need not manifest itself at birth, but weakness may be inherent as a homochronous form of hereditary transmission, and come to expression without any auxiliary moment (as in hereditary degeneration of the macula), or, probably, by inducing such moments as endocrine dysfunction, with mesenchymal weakness. With regard to the latter, it is worthy of mention that in 1 of the cases

89. Ellis, J. W.: Keratoconus with Demonstration of Cases, Texas State J. Med. **20**:327, 1924.

90. Stähli, J.: Das Krankheitsbild des Keratokonus vom Standpunkte der Variabilitätslehre mit zwei klinischen Beispielen vom Familiarität des Keratoconus und einem Anhang mit Bemerkungen zur Myopiefrage, Klin. Monatsbl. f. Augenh. **62**:712, 1919.

in the pedigree of van der Hoeve, with unquestionable recessive hereditary involvement, the Abderhalden test gave a positive reaction to thyroid. The clinical observation of progressiveness of a preexisting conical cornea during pregnancy may serve as another illustration.

The possibility remains that conical cornea is a clinical entity, either hereditary or acquired, without hereditable characteristics, based on pathologic changes in the endocrine gland. The association of conical cornea with mongolism raises important problems. In both conditions an endocrine disturbance, possibly polyglandular, may be operative, either primary or as a result of a general developmental abnormality in the germ plasm. The occurrence of conical cornea in cases of mongolism permits the conclusion that the nonhereditable form of keratoconus must be associated with endocrine imbalance characteristic of mongolism and, furthermore, that in the complex transmission of the anomaly the genetic factors may influence the cornea directly or through a possible inherited dysfunction of the endocrine glands.

31 Lincoln Park.

Book Reviews

Children's Eye Nursing. By James Hamilton Doggart, M.A., M.D., F.R.C.S. Price, 9s. 6d. Pp. 144, with 93 illustrations, 13 in color. London: Henry Kimpton, 1948.

The pediatric nurse has certain problems and consequent technics differing somewhat from those of her sister in general nursing. There are also a few disparities between the work of a nurse who takes care of children's eyes and that of her colleague who performs a like function for adults. To meet this situation, Doggart has written a little volume which he thinks "can be of some help." There are chapters on anatomy, etiology, inflammations, squint, injuries, instruments and dressings; but it must be admitted that the book overflows the limits inherent in its title. The format is convenient, and the illustrations are clear.

G. M. Bruce, M.D.

Transactions of the Ophthalmological Society of Australia (British Medical Association). Volume 7. Price, 15s. Pp. 143, with 17 illustrations. Sydney, Australia: Australasian Medical Publishing Company, Ltd., 1947.

This volume comprises the transactions of the 1947 meeting of the Australian Ophthalmological Society. The president's address, delivered by D. A. Williams, was a résumé of the history of ophthalmology in Australasia. N. M. Macindoe reported on the results of a visit that he made to Europe and the United States. He discussed the work that he observed on permeability of the cornea, retrobulbar neuritis and visual acuity at Harvard; virus diseases and corneal grafting, at Johns Hopkins; color vision and lighting standards, at the Institute of Ophthalmology in New York; biochemistry of the ocular media, in Basel; corneal distortions, subjective screens, content of the aqueous, permeability of the ciliary body and tonometry, at Zurich; perimetry, at Berne; strabismus, at London; electroretinography and monochromatic light, at Stockholm, and colloidometry, at Copenhagen. He states that Australia is lagging seriously behind other countries in the training of qualified ophthalmic surgeons.

J. B. Hamilton, who has been continuing his work on dry eyes, reported 24 additional cases. In his paper on "Protection of the Eyes in Industry," A. L. Tostevin classified industrial accidents on the basis of cause and of the agent responsible. W. L. Gibson has had a radon seed made in the form of a circle, so that it can easily be sutured to the globe in cases of retinoblastoma. He stated the belief that the maximum surface dose is 7,000 r and the average tumor dose 4,000 r. Two cases of intraocular tumor, a melanoma of the choroid of four years' duration and a retinoblastoma with extension, were reported by Kevin O'Day. The article is accompanied with excellent photomicrographs.

J. A. O'Brien, reporting on 60 cases in which the Lagrange operation was performed, stated that in his opinion this procedure presents

fewer complications and offers a higher percentage of successes than any other. A case of endothelial dystrophy was presented by C. S. Colvin. It is interesting to note that the frequency of this disease, not uncommon in the United States, is about 1 to 100,000 in Australia. In the treatment of dendritic ulcer, Frank Phillips cleans the little knobs on the ulcer with a dental drill and uses dry blotting paper around the infected region to wipe off the epithelium. He then uses atropine and a bandage.

Lennox Price reported 2 consecutive cases of nonmagnetic metallic intraocular foreign bodies removed by means of forceps introduced into the vitreous. The first eye was saved without much vision, but the second eye was lost from panophthalmitis. R. G. Banks-Smith reported a case of partial thrombosis of the central retinal vein treated with dicumarol. The patient was admitted to the hospital, where the prothrombin time could be estimated. Three hundred milligrams of dicumarol was given as the initial dose; then 200 mg., for the next two days; then a dose of 100 mg. was repeated for a while. He stated the belief that this anticoagulation therapy prevented complete occlusion of the vessel.

Optic neuritis following measles was discussed by T. C. Meurer, with presentation of 3 cases. In all these cases disks were pale, but useful vision was finally obtained. Vision improved to 6/9 or better within twelve months.

Papers on orthoptics were read by Emmie Russell, J. A. Pockley and Diana Mann. Miss Russell stated the belief that the symptoms of the exophorias are easily relieved, that hyperphorias respond only fairly well and that the best results are obtained with convergence insufficiencies. Pockley stated: "Long-continued, uncontrolled treatment by the orthoptist can easily be an evil and I think many orthoptists will agree that an operation at the right time may shorten the period of treatment dramatically. Conversely, unexpected progress may cause the surgeon to modify or to abandon his plan for operation." Miss Mann stated the belief that normal binocular vision is developed in the first two years of life; if it is not developed then, no subsequent training can make amends. Any divergent squint, she asserted, tends to recur under certain conditions, and constant convergent squints are never corected without operation.

Arthur D'Ombrain discussed his personal experience with allergic sensitivity to procaine hydrochloride. He now uses as a substitute the following solution, which he finds effective and safe:

Cocaine hydrochloride	0.75%
Epinephrine chloride	1: 50,000
Chlorobutanol	0.50%

The final paper was a survey of ophthalmic diseases in western New South Wales, by K. B. Redmond. Forty-eight conditions were investigated in his preliminary survey. As might be expected, refractive errors were the most frequently observed, and after that, conjunctivitis, injuries, pterygium and strabismus.

This volume is additional evidence of the high level that has been attained by Australian ophthalmology.

G. M. Bruce, M.D.

Refraction of the Eye. By Alfred Cowan, M.D. Third Edition. Price, $5.50. Pp. 287, with 187 illustrations and 3 colored plates. Philadelphia: Lea & Febiger, 1948.

Dr. Cowan's "Refraction of the Eye" is so well known (ARCH. OPHTH. **34**:172 [Aug.] 1945) that it needs no comment except to welcome its appearance in a third edition and to state that this new edition has been revised and brought up to date. The book merits its well deserved popularity; as a comprehensive and practical treatise, it is of great service to students of ophthalmology.

ARNOLD KNAPP.

Collected Reprints from the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital. July 1945 to December 1947. Volume 8, Baltimore, 1948.

Volume 8 includes the reprints of the articles by the members of the staff of the Wilmer Ophthalmological Institute which appeared between July 1945 and December 1947; 50 articles and the titles of 12 other publications are listed. This imposing collection covers a wide range of subjects and exemplifies the industry and ability of this excellent group, working under the supervision of the director, Dr. Alan C. Woods.

ARNOLD KNAPP.

The W. H. Ross Foundation (Scotland) for the Study of Prevention of Blindness. London: University of London Press, Ltd., 1948.

This volume is a compendium of papers which have been published as the result of grants made by this foundation. The papers are of widespread ophthalmologic interest and for the most part have to do with injuries and infections of the cornea, especially those encountered in industrial practice. A list of the titles and their authors follows:

A. J. Rhodes: Conjunctival Bacteria and Hypopyon Ulcer
Studies on the Bacteriology of Hypopyon Ulcer

R. M. Dickson: Traumatic Ulcer of the Cornea, with Special Reference to Coal Miners
First-Aid Treatment of Industrial Eye Injuries
Eye Injuries in Industry
A Statistical Analysis of Persons Certified Blind in Scotland

Dorothy Adams Campbell: Hereditary Microphthalmia in Albino Rats

Joseph R. Mutch and Donald Mackay: The Detection and Significance of Melanophore-Expanding Substance in Urine and Blood, with Special Reference to Retinitis Pigmentosa

J. M. Robson and G. I. Scott: Local Treatment of Experimental Pyocyaneus Ulcers of the Cornea with Albucid Soluble

J. M. Robson and Walter Tebrich: Peneetration of a Water-Soluble Sulphonamide (Albucid Soluble) into the Eyes of Rabbits
Penetration and Distribution of Sodium Sulphacetamide in Ocular Tissues of Rabbits

J. M. Robson and G. I. Scott: Local Effectiveness of Sodium Sulphacetamide (Albucid Soluble) in Treatment of Experimental Ulcers of the Cornea

Effect of Certain Chemotherapeutic Agents on Experimental Eye Lesions Produced by Staphylococcus Aureus

Local Chemotherapy in Experimental Lesions of the Eye Produced by Staphylococcus Aureus

J. M. Robson: Experimental Corneal Ulcers

J. M. Robson and G. I. Scott: The Production and Treatment of Experimental Pneumococcal Hypopyon Ulcers in the Rabbit

Experimental Streptococcal Lesions of the Rabbit's Eye and Their Treatment

Proflavine and Corneal Injection

M. Ginsberg and J. M. Robson: The Effect of Detergent on the Penetration of Sodium Sulphacetamide (Albucid Soluble) into Ocular Tissues

T. P. Duguid, M. Ginsberg, I. C. Fraser, J. Macaskill, J. C. Michaelson and J. M. Robson: Experimental Observations on the Intra-Vitreous Use of Penicillin and Other Drugs

Arnold Loewenstein and John Foster: Contribution to Knowledge of Ocular Siderosis and Posterior Degenerative Pannua